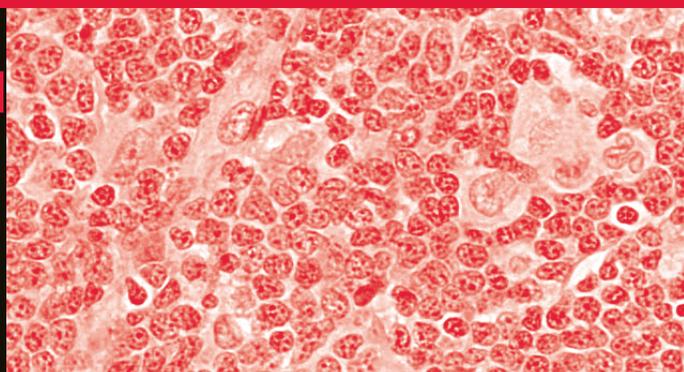


R E S E A R C H
Report



ASH 2018 Annual Meeting: Expanding the Landscape of Lymphoma Therapies

Lymphoma is a complex disease, comprised of more than 90 subtypes. Though recent improvements in therapies such as targeted agents and immunotherapies have allowed many patients to survive their lymphoma, patients with less common subtypes and those whose disease relapses, becomes resistant to therapy, or doesn't respond to therapy still have poorer rates of overall survival. At the 2018 Annual Meeting of the American Society for Hematology (ASH), much of the lymphoma research presented focused on patient populations with poorer outcomes, whether through the development of new first-line therapies for rare subtypes, or through a further refinement of treatment strategies for a high-risk group in a more common subtype.

Celebrating its 60th year as the preeminent global conference for hematologists, oncologists, and researchers across the hematologic malignancies, the ASH Annual Meeting offers a crucial forum for international discussion of new research and its implications for patient care. Each year, more than 20,000 researchers attend the Annual Meeting, and more than

ASH Annual Meeting Highlights	
CAR T-Cell Research Updates Long-term clinical trials data and new targets	Pg.3
New Therapies and Combinations New therapy types and new combinations of existing therapies	Pg. 5
Rare Subtypes Promising data for CNS, T-cell, and Marginal Zone lymphomas	Pg. 7
Health Services Research Addressing survivor needs and CLL patient treatment choices	Pg. 9
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3,000 abstracts are presented, including contributions from Lymphoma Research Foundation (LRF) grantees, Scientific Advisory Board (SAB) members, and members of its research colloquia and professional education steering committees. For the 2018 meeting, over 550 abstracts were authored by at least one

LRF-affiliated scientist. Additionally, 43 of the Foundation's 45 current SAB members and 142 LRF grantees contributed to at least one abstract.

"The Lymphoma Research Foundation has always sought to support researchers conducting the most innovative, impactful

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CAR T-Cell Therapy for Lymphoma

Immunotherapy enhances the power of a patient's immune system to attack tumors. An immunotherapy approach, called chimeric antigen receptor (CAR) T-cell therapy, uses patients' own immune cells to treat their cancer.

FEATURED IN THIS ISSUE: New CAR T-cell Therapy Education Materials **Page 8**

Lymphoma Research Foundation scientists have developed new resources for patients and their caregivers interested in learning more about CAR T-cell immunotherapy.

LETTER FROM THE CEO



Dear LRF Friends and Supporters,

The annual meeting of the American Society of Hematology (ASH) brings together international experts in hematology to review thousands of scientific abstracts and research papers focused on the study and treatment of lymphoma. I had the opportunity to attend the meeting in San Diego, California in December, and was excited to see the diversity of data expanding the treatment landscape for lymphoma patients, both in a range of new therapeutic strategies as well as in the number of promising results for rare and high-risk lymphomas. This edition of *Research Report* features highlights from those new studies, many of which featured contributions from Lymphoma Research Foundation grantees and scientific leadership.

One of the most significant lymphoma clinical trials presented at ASH was the ECHELON-2 study, which has been called practice-changing for peripheral T-cell lymphoma patients. LRF is proud that SAB member Steven Horwitz, MD, of Memorial Sloan Kettering Cancer Center, was lead author on this study. An exploration of this study and what the term “practice-changing” means for lymphoma patients may be found on page 4.

Additionally, the promising data available for CAR T-cell therapy (highlights begin on page 3), has prompted considerable interest in this therapy from lymphoma patients and their caregivers. The Foundation has developed a range of new educational materials and programming to answer patient questions and concerns about this unique class of therapy. For more details, please see page 8.

This special edition of *Research Report* allows us to highlight the results of your support for lymphoma research. Thank you for all you do in helping the Foundation advance innovative research and improve care for all who are impacted by a lymphoma diagnosis.

Sincerely,

Meghan Gutierrez
Chief Executive Officer

Team LRF Spotlight: Annual Boca Raton Luncheon

LRF hosted its Annual Luncheon at St. Andrews Country Club in Boca Raton, FL on February 4, 2019. More than 250 members of South Florida’s philanthropic community attended the bespoke fashion event that served up special Spring 2019 looks from various brands, in support of LRF and its mission.

The Luncheon’s keynote address was delivered by Andrew Zelenetz, MD, PhD, of Memorial Sloan Kettering Cancer Center, and Chair-Elect of LRF’s Scientific Advisory board, who provided updates on lymphoma research and treatments to the dedicated group. Since 2007, the Annual Luncheon has raised more than \$1.6 million on behalf of the Lymphoma Research Foundation, including more than \$155,500 raised with this year’s event.



(L) Event Co-Chairs Joan Hauser, Mitzi Oremán, Gloria Klein, Gladys Cook, Judy Bronsteen, Toby Cooperman, Elisabeth Dalfen. (R) Errol Cook and LRF Chair-Elect Andrew Zelenetz, MD, PhD of Memorial Sloan Kettering Cancer Center

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research in lymphoma," said Thomas M. Habermann, MD, of Mayo Clinic, Chair of the LRF Scientific Advisory Board. "It is exciting to see the number of Scientific Advisory Board members, grantees, and members of our research consortia bringing significant research results to the ASH Annual Meeting, and we look forward to seeing these results improve outcomes for lymphoma patients."

This special issue of *Research Report* covers highlights from the 2018 ASH Annual Meeting, focused on the topic areas in the table of contents on the front cover.

CART-cell Research Results Reflect Continued Promise

Continuing the trend of the past several years, the 2018 ASH Annual Meeting included a number of studies investigating chimeric antigen receptor (CAR) T-cell therapy in various subtypes of lymphoma. An immunotherapy that uses a patient's own T-cells, altered to specifically attack cancer cells and then reintroduced to the patient, CAR-T-cell has shown promising early results for aggressive lymphomas that have proven resistant to other therapies. [For more on the basics of CAR T-cell therapy, see page 8 for coverage of the Foundation's new CAR-T cell education materials.] With several years of clinical trials data now available, researchers are beginning to report both long-term results and a greater understanding of the biological mechanisms that make this therapy effective.

Updated results from the JULIET trial, testing tisagenlecleucel (Kymriah) in relapsed or refractory diffuse large B-cell lymphoma (DLBCL), revealed encouraging long term results. Of the 99 patients who were tracked and evaluated for the main

portion of the study, the overall response rate was 54 percent, with 40 percent of patients reaching a complete response (no detectable disease). Researchers, including first author Stephen Schuster, MD, of the University of Pennsylvania, a founding member of the Foundation's Philadelphia Lymphoma Rounds steering committee, noted that the possibility of being relapse free at six months after treatment was 66 percent, a level which stayed consistent through to 18 months (64 percent). Additionally the researchers observed no relapses beyond 11 months post treatment, indicating a very durable and lasting response for the patients that reach that milestone. The researchers further noted that results were consistent across all patients, even those, such as elderly patients, that report poorer prognosis on other available treatments, indicating that tisagenlecleucel is an effective therapy with sustainable results for patients who may have few other options.

► *This study also features contributions from LRF Scholar Jason Westin, MD, of MD Anderson Cancer Center and MCL Consortium member Koen van Besien, MD, PhD, Weill Cornell Medicine.*

Similarly, researchers on the ZUMA-1 trial reported two-year follow-up data for their study of axicabtagene ciloleucel (Yescarta) in large B-cell NHL. The study, which included patients with DLBCL, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma (FL), reported data from 101 patients treated in late 2015 and early 2016; 84 percent of these patients achieved some response to treatment, while 58 percent had a complete response. Researchers noted that the group had not yet reached median overall survival (the point at which exactly 50 percent of a patient cohort has survived following treatment, a common milestone for determining the effectiveness of a therapy), and concluded that, with a median

overall survival greater than two years, axicabtagene ciloleucel is a durable and effective therapy for aggressive relapsed or refractory B-cell lymphomas.

► *This study featured contributions from LRF Grantees Alex Herrera, MD, of City of Hope, Patrick Reagan, MD, of Wilmot Cancer Institute, University of Rochester, and John M. Timmerman, MD (also a current SAB member) of the University of California, Los Angeles David Geffen School of Medicine, as well as former SAB member Andre Goy, MD of John Theurer Cancer Center and MCL Consortium Member Ian Flinn, MD, PhD of Sarah Cannon Research Institute.*

In addition to the aforementioned CAR T-cell therapies which have received approval from the U.S. Food and Drug Administration (FDA) for certain B-cell lymphomas, researchers continue to develop and evaluate additional therapies in this class. A study of CD19 specific CAR T-cell therapy JCAR014 and concurrent ibrutinib (Imbruvica) in relapsed and refractory chronic lymphocytic leukemia (CLL) patients reported early phase clinical results that researchers called "the most encouraging results seen to date" for a combination of CAR-T-cell and a targeted agent. Nineteen patients with CLL were given ibrutinib before, during, and after their CAR-T therapy for at least three months; their results were then compared to the outcomes of an earlier group of CLL patients treated with ibrutinib initially before receiving CAR-T-cell therapy while discontinuing the ibrutinib. Eighty-three percent of the patients who received concurrent ibrutinib and CAR-T-cells reported complete or partial responses, compared to 65 percent of patients who did not receive concurrent ibrutinib. Researchers further noted that in the concurrent arm they did not observe a single severe case of cytokine release syndrome (CRS), a side effect common to immunotherapies that may cause fever, nausea, headache, low

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ECHELON-2 Trial Demonstrates “Practice-Changing” Results for Peripheral T-Cell Lymphomas

Numerous abstracts and studies presented during the American Society of Hematology (ASH) Annual Meeting - one of the largest and most prestigious scientific meetings in the world - offer new solutions to challenges in diagnosing and treating the different subtypes of lymphoma. Clinical trial results may confirm earlier, smaller studies with a more robust set of data. Laboratory studies may identify a new biomarker or demonstrate how biomarkers contribute to the growth of cancer cells. But only a small number of significant studies receive the designation of “practice changing” from the researchers who present them. Practice changing research, generally resultant from clinical trials, is anticipated to change the standard clinical practice for a particular diagnosis.

At the 2018 ASH Annual Meeting, “practice changing” was used to describe the results of the ECHELON-2 study, which was presented by Lymphoma Research Foundation (LRF) Scientific Advisory Board member Steven Horwitz, MD of Memorial Sloan Kettering Cancer Center. The large, multicenter study of 452 patients with previously untreated CD30 positive peripheral T-Cell lymphoma (PTCL) randomly assigned patients to either the standard chemotherapy regimen, CHOP, (cyclophosphamide, doxorubicin, vincristine, and prednisone), or brentuximab vedotin (Adcetris) plus chemotherapy with cyclophosphamide, doxorubicin and prednisone (A+CHP). In the A+CHP group, median progression-free survival was 48.2 months compared to 20.8 months in the CHOP group. Importantly, this improvement in progression free survival translated into a significant improvement in overall survival, with a 77 percent probability of survival three years following treatment for those treated with A+CHP.

Dr. Horwitz notes that ECHELON-2 is the first study in patients with PTCL to show an improvement in overall survival over a standard therapy such as CHOP, and that the significant benefit indicates that oncologists should strongly consider adopting this combination therapy for patients eligible for this approach. “This study is exactly what we mean when we say practice-changing,” says Dr. Horwitz, “because it shows a vast improvement on the current standard of care for initial treatment of peripheral T-cell lymphoma, which had not significantly changed in decades.”



Steven Horwitz, MD, of Memorial Sloan Kettering Cancer Center, presented the ECHELON-2 results at the 2018 ASH Annual Meeting.

The results of the ECHELON-2 study resulted in the U.S. Food and Drug Administration (FDA) approving the A+CHP regimen for previously untreated anaplastic large cell lymphoma (ALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL). Reviewed under the FDA’s Real-Time Oncology Review Pilot Program, it received approval less than two weeks after the application was fully submitted. Dr. Horwitz adds, “With the FDA approval, the brentuximab vedotin + chemotherapy regimen should become a new standard of care for newly diagnosed PTCL whose tumors express CD30.”

For additional information on PTCL, including the latest treatment information, visit the LRF Peripheral T-Cell Lymphoma Learning Center at lymphoma.org/PTCL.

➤ *This study also included contributions from LRF Scientific Advisory Board Members Ranjana Advani, MD, of Stanford University, Nancy Bartlett, MD, of Washington University in St. Louis, Owen O’Connor, MD, PhD, of Columbia University Medical Center, Barbara Pro, MD, of Northwestern University, Kerry Savage, MD, of British Columbia Cancer, and LRF grantee Kunihiro Tsukasaki MD, PhD, of Saitama Medical University (Japan).*

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blood pressure, and breathing difficulties. Although noting larger and randomized studies should be conducted to confirm these results, the researchers concluded that the higher response rate and decrease in severe CRS made concurrent ibrutinib and CART-cell therapy a promising treatment strategy for relapsed/refractory CLL.

► *This study included contributions from LRF grantees Ryan Cassaday, MD and Brian Till, MD, as well as former SAB member David Maloney, MD, PhD, all from Fred Hutchinson Cancer Research Center, University of Washington.*

To date most of the CAR T-cell therapies tested in lymphoma (including both types that have received FDA approval) consist of CD19 CART-cells – T-cells which are engineered to target the CD19 receptor protein, a common protein in B-cell NHL. However in Hodgkin and some T-cell lymphomas, the protein CD30 is far more common, prompting the development of CD30 CART-cells in order to test the efficacy of this immunotherapy in a broader range of subtypes. Researchers from the University of North Carolina, Chapel Hill and Levine Cancer Institute presented preliminary results from an early clinical study of CD30 CAR T-cells in relapsed or refractory Hodgkin and T-cell lymphomas. Sixteen patients with HL, one with enteropathy associated T-cell lymphoma, and one with Sézary syndrome were enrolled. The median number of previous therapies received by the group was 8.5, including a number of patients who had received either autologous or allogeneic stem cell transplant. Fourteen patients were evaluable for efficacy, with six complete responses (43 percent), one partial response, and two with stable disease. Two of the 14 patients remain in complete response at one year following treatment. The

researchers further found that a higher dose of CART-cells was more effective of the two dose levels tested, and that patients receiving bendamustine and fludarabine chemotherapy prior to CAR T-cells sustained longer progression free responses than patients receiving bendamustine alone, suggesting an effective treatment regimen around which to build future trials.

New Therapies and Therapeutic Combinations

New targeted therapies also reported promising early data at the ASH Annual Meeting. The targeted agent cerdulatinib inhibits the SYK and JAK pathways that can promote the growth of peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL). A small scale study of 60 patients (38 with PTCL and 22 with CTCL) who had received at least one prior therapy prior to receiving cerdulatinib presented initial data. In the PTCL cohort, 26 patients were evaluable for response, with an overall response rate of 35 percent (nine patients), with eight of those patients achieving a complete response. In the CTCL cohort, ten patients were evaluable for response, with an overall response rate of 50 percent (five patients), with one of those patients achieving complete response. Steven Horwitz, MD, of Memorial Sloan Kettering Cancer Center, who presented the data, noted that patients with mycosis fungoides and Sézary syndrome were among those who responded to the therapy. Dr. Horwitz noted that this encouraging early data, including the wide spectrum of PTCL and CTCL subtypes that responded to the therapy, will aid the design of a larger scale clinical trial of cerdulatinib in T-cell lymphomas.

► *This study included contributions from Scientific Advisory Board member Sonali M. Smith, MD, of The University of Chicago, and MCL Consortium member Tycel Phillips, MD, of University of Michigan Cancer Center.*

Bispecific antibodies, a type of manufactured antibody that can bind to two different types of proteins expressed by cells, are beginning to be explored throughout blood cancers. In lymphoma, an early study of mosunetuzumab, which redirects normal T-cells to kill malignant B-cell lymphomas by binding to CD3 on T-cells and CD20 on B-cells, reported early results on efficacy and safety in relapsed and refractory B-cell NHL. Presented by MCL Consortium member Lihua Elizabeth Budde, MD, of the City of Hope, patients were assigned to one of two groups, which each received mosunetuzumab; group A received the therapy on the first day of a three-week cycle while group B received increasing doses of the therapy on day 1, 8 and 15 in the first cycle, before a dose on day 1 for every subsequent cycle. Sixty-six patients had at least a three month follow up and were able to be evaluated for efficacy – of these 41 percent (27 patients) had an objective response, including 61 percent (11 of 18) FL patients and 33 percent (13 of 39) DLBCL patients. Eighteen patients (27 percent) had a complete response, including 50 percent (9 of 18) of the FL patients. Some of the patients who responded to therapy had relapsed following CART-cell therapy, indicating mosunetuzumab may be an option even where CAR T-cell fails. Dr. Budde also noted that most side effects were low-grade and occurred at lower rates than many current therapies, including CAR T-cell. The researchers are continuing with the current trial to identify the optimal dose and treatment schedule for mosunetuzumab; additional trials to look at this agent in combination with chemotherapy and other targeted agents are also in progress.

► *This study also included contributions*

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from LRF Scientific Advisory Board members Nancy Bartlett, MD, of Washington University in St. Louis, Laurie Sehn, MD, of British Columbia Cancer, and MCL Consortium member Ian Flinn, MD of Sarah Cannon Research Institute.

Catherine Diefenbach, MD of New York University, a past recipient of LRF's Clinical Investigator Career Development Award, presented data from cooperative group ECOG-ACRIN's clinical trial of a new combination of existing therapies ipilimumab (Yervoy), nivolumab (Opdivo) and brentuximab vedotin (Adcetris) for relapsed and refractory Hodgkin lymphoma. The combination therapy, combining checkpoint inhibitor immunotherapy (nivolumab), with a monoclonal antibody currently approved for melanoma (ipilimumab), and a targeted CD30 inhibitor (brentuximab vedotin), was designed to activate the immune cells in the tumor micro-environment, while overcoming tumor resistance with brentuximab vedotin. Twenty-two patients were enrolled on the study, which sought data on both the safety and efficacy of the treatment regimen. Three patients discontinued therapy due to severe side effects, and researchers also noted a higher incidence of grade 3 side effects than trials of only two of the three drugs, but most patients were able to complete their therapy. Of the 19 patients evaluable for response, the overall response rate was 95 percent (18 of 19) with a complete response rate of 79 percent (15 of 19). With median follow-up periods of less than a year thus far, neither progression free survival or overall survival had been reached. Dr. Diefenbach noted that in a patient population that had received numerous other therapies, with nine patients who had already gone through



L. Elizabeth Budde, MD, PhD, of the Beckman Research Institute, City of Hope, presents at the 2018 North American Educational Forum on Lymphoma. Dr. Budde's research is featured on pages 5 and 7.

stem cell transplant and relapsed, an overall response rate of 95 percent was extremely promising. A larger randomized trial comparing this triplet combination to the doublet of brentuximab vedotin and nivolumab is ongoing.

► This study also included contributions from LRF SAB members Ranjana Advani, MD of Stanford University, Stephen Ansell, MD, PhD of Mayo Clinic, and Brad Kahl, MD of Washington University in Saint Louis, as well as LRF grantees Jonathon B. Cohen, MD, MS of Emory University, Reem Karmali, MD, of Northwestern University, MCL Consortium member Timothy Fenske, MD, of Medical University of Wisconsin, and former SAB member Richard F. Ambinder, MD, of Johns Hopkins University.

A clinical trial funded by an LRF Chronic Lymphocytic Leukemia Grant presented intriguing results for a drug commonly used to treat malaria. Senior author David A. Frank, MD, PhD, of Dana-Farber Cancer Institute, received a CLL Research Grant from LRF in 2009 for a trial of STAT3 inhibitor pyrimethamine (Daraprim) which was presented by Jennifer R. Brown, MD, PhD, herself a past LRF

grant recipient. While noting that the trial data was accrued prior to the availability of ibrutinib and other targeted agents for CLL, the researchers noted STAT3 inhibition could lead to fewer side effects than other types of therapy, since normal cells are able to tolerate a loss of STAT3 function in a way cancer cells cannot. Sixteen relapsed CLL patients were enrolled on the study; although no objective responses were observed, half of patients achieved stable disease. The researchers noted that tests of patient plasma revealed that only in the highest dose cohort did patients have enough concentration of pyrimethamine to consistently inhibit STAT3, and suggested that further trials with higher dose levels may be needed. Additionally, pyrimethamine's STAT3 inhibition may be more effective when combined with other therapies. Further studies in both CLL, other lymphomas, and non-lymphoid cancers are ongoing.

► This study also included contributions from LRF grantee Catherine Wu, MD of Dana-Farber Cancer Institute.

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Results for Rare Subtypes

Several lymphoma subtypes which are less common and have poorer outcomes saw significant and promising results reported at the 2018 Annual Meeting.

Central nervous system lymphoma (CNSL) occurs in two forms – primary (PCNSL), in which the patient's lymphoma originates in the central nervous system (brain and spine), and secondary (SCNSL), in which a patient with DLBCL relapses in the central nervous system. Both types are difficult to treat because of the blood-brain barrier, a lining of cells around the brain that is supposed to prevent toxins or pathogens from reaching the brain. Unfortunately, it also can prevent certain drugs intended to treat cancerous cells from reaching their targets in the brain or nervous system, including many standard lymphoma therapies.

Ibrutinib (Imbruvica) has demonstrated an ability to cross the blood-brain barrier, leading researchers to hope it will be an effective treatment for CNSL patients. Christian Grommes, MD of Memorial Sloan Kettering Cancer Center, presented results from a trial of ibrutinib in recurrent/refractory PCNSL and SCNSL. Of the forty patients for whom data was available at the ASH Meeting, 31 patients (78 percent) reported a response – including 81 percent (22 of 27) of patients with PCNSL. Median progression-free survival (PFS) was four months, although patients who were able to tolerate at least 15 days of treatment reached a median PFS of over five months. Dr. Grommes, who received a 2012 LRF Clinical Investigator Career Development Award for separate research in PCNSL, noted that three patients stopped treatment due to severe grade side effects, but that 24 patients did not report any severe grade side effects. With a high rate of response and most

patients reporting a manageable level of side effects, ibrutinib seems to be a promising strategy for CNSL patients.

Researchers from City of Hope presented results of a laboratory study of CAR T-cells in CNSL, which also had promising implications. Seeking to directly compare CAR T-cell therapy's effectiveness in both CNSL and systemic lymphomas (lymphomas occurring in the lymphatic system, which include most common lymphomas), the researchers created a mouse model with both CNS and systemic lymphoma, which were then given CAR T-cells in one of two ways, intracerebroventricular (ICV), or into the brain stem to bypass the blood-brain barrier, and intravenous injection (IV) to target the systemic lymphoma. The researchers noted that they repeatedly found that one ICV infusion was able to completely eradicate both the CNS and systemic lymphoma by two weeks after treatment and that 100 percent of their mice remained tumor free for 300 days (at which point the experiment ended). By contrast the IV infusion resulted in delayed anti-tumor activity with complete remissions occurring about 40 days post treatment and relapses occurring before 180 days. Additional experiments done to track the T-cells found that ICV CAR T-cells were able to efficiently expand outside the CNS and reach systemic tumor locations, explaining their effectiveness. Though in-human trials will need to be conducted, the researchers concluded that these results suggest not only that CAR T-cells may be effective in CNS lymphomas but that one treatment could be effective for both CNS lymphoma and systemic lymphoma, a common occurrence for secondary CNS lymphoma patients.

► *This study included contributions from LRF grantees Leslie Popplewell, MD, and Stephen J. Forman, MD (also a former LRF SAB member), as well as MCL Consortium member L. Elizabeth*

Budde, MD, PhD, all of City of Hope.

Former SAB Chair John Leonard, MD of Weill Cornell Medicine presented results from the AUGMENT study for relapsed and refractory indolent NHL. Though FL patients represented the majority enrolled on the study, more than 60 participants had marginal zone lymphoma (MZL), a rarer form of B-cell NHL. The multicenter study randomized patients to either the control arm of rituximab and a placebo or lenalidomide plus rituximab (R2). Of the 358 patients enrolled, progression free survival for the R2 group was 39.4 months versus 14.1 months for the control. The R2 group also reported superior overall response rate (78 percent to 53 percent) and complete responses (34 percent to 18 percent). Dr. Leonard also noted that though certain hematologic side effects were more common in the R2 group, the improved efficacy and longer time to disease progression for that cohort allowed 71 percent of the R2 patients to complete all twelve cycles of treatment versus 61 percent of the control group. Both MZL and FL patients saw improvement on the combination therapy, making this a promising new treatment option for both subtypes.

► *This study also included contributions from former SAB member Nathan H. Fowler, MD, of MD Anderson Cancer Center, and MCL Consortium Member Ian Flinn, MD, PhD, of Sarah Cannon Research Institute.*

Reflecting the growing research interest in marginal zone lymphoma, the Lymphoma Research Foundation is convening a Marginal Zone Lymphoma Scientific Workshop in April 2019, one of the first scientific programs in the United States focused exclusively on MZL. A report from this workshop will appear in the Summer 2019 *Research Report*.

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Foundation Expands Educational Resources on CAR T-Cell Therapy

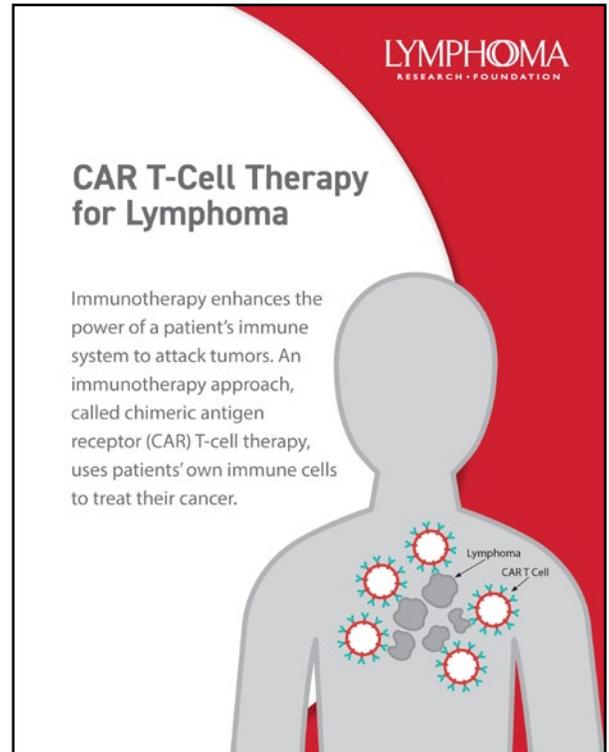
As chimeric antigen receptor (CAR) T-cell therapy continues to report promising results for some lymphoma patients (see page 3), the Lymphoma Research Foundation has developed a range of new resources for patients and caregivers seeking to understand how this groundbreaking new therapy works and what effects undergoing CAR T-cell treatment may have on their disease and quality of life.

CAR T-cell therapy is a type of immunotherapy which extracts and then engineers a patient's own T-cell immune cells with chimeric antigen receptors (CAR) designed to recognize particular proteins common to certain subtypes of lymphoma cells. Once reintroduced to a patient's system, the CAR T-cells bind with the lymphoma cells and begin to destroy them. Current clinical trial results suggest that CAR T-cell therapy can be particularly effective for patients with aggressive blood cancers that are resistant to other therapies.

The Lymphoma Research Foundation's new CAR T-cell fact sheet, developed in collaboration with medical reviewers Jeremy S. Abramson, MD, of Massachusetts General Hospital, and Foundation Scientific Advisory Board members Nancy Bartlett, MD, of Washington University in Saint Louis, and Ann LaCasce, MD, of Dana-Farber Cancer Institute, seeks to provide patients and caregivers with easy to understand explanations of how CAR T-cell therapy works, possible side effects, and other considerations. An electronic version is [available on the LRF website](#); print copies may be obtained by contacting the LRF Helpline.

Additionally, recordings of recent patient education programs focused on CAR T-cell therapy are also available through the Foundation's website and YouTube channels:

- In April 2018, LRF hosted a Facebook Live chat on CAR T-cell therapy with Dr. Jeremy Abramson and Dr. Caron Jacobson. [Video of the 48 minute discussion](#) is on the LRF YouTube channel [and LRF website](#).
- The 2018 North American Education Forum on Lymphoma's session on CAR T-cell therapy, featuring Elizabeth Budde, MD, PhD, of City of Hope and Caron Jacobson, MD, of Dana-Farber Cancer Institute, is a [30 minute presentation](#) also available on the YouTube channel [and LRF website](#).



- The November 2018 teleconference "Update on CAR T-cell Therapy for People Living with Lymphoma," offered in partnership with CancerCare, is available as audio download or webcast (audio with presenter slides) [on the CancerCare website](#). This hour-long program features Dr. Nancy Bartlett as well as M. Lia Palomba, MD, of Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine.

"Access to information is critical to lymphoma patients accessing quality care, because an educated patient is an empowered patient," said Peggy Ann Torney, LRF Chief Strategy, Communications, and Engagement Officer. "The Lymphoma Research Foundation is committed to providing patients and caregivers access to the most up-to-date and expert information about their disease and treatment options, so that they can have the information needed to understand new and emerging treatment options, like CAR T-cell therapy, and how they may impact their lymphoma experience."

For assistance accessing the Foundation's CAR T-cell or other patient education resources visit lymphoma.org/learn or contact the Helpline at helpline@lymphoma.org or 800-500-9976.

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Health Services Research

In addition to clinical trials, clinical research often encompasses questions about what demographic, societal, or environmental factors could contribute to a person's increased risk for disease or poorer outcomes. Health services research, which studies how social factors, organizational structures, and demographic factors affect access, cost, quality, and outcomes of health care, allows researchers to go beyond new therapies for strategies to improve patient outcomes.

A health services qualitative study to investigate the needs of lymphoma survivors and caregivers was presented in a poster session with senior author Christopher Flowers, MD, a LRF SAB member from Winship Cancer Institute, Emory University. The researchers noted that the high cure rate for HL and the growing number of NHL patients who survive ten years or longer has resulted in a dramatic growth in lymphoma survivors, many of whom are often struggling with adverse effects from their cancer treatment. In a series of focus groups—some held concurrently with LRF patient education programs—and phone interviews, the researchers asked patients about their experiences, opinions, and priorities for lymphoma care and research. They noted that many patients felt there was a lack of information and communication from their clinical care teams, while caregivers felt like their needs went completely unaddressed during the care process. Many participants expressed great interest in research, but had difficulty finding results and studies relevant to them as survivors, particularly those which could guide their decisions on quality of life

post-treatment, such as diet and emotional or mental health. The researchers also found many participants reported strengthened relationships with their loved ones and increased spirituality or mindfulness as benefits from their experiences as cancer patients. They concluded that the findings from this study could be used to help identify the unmet needs of lymphoma survivors and their caregivers, including identifying areas for research to help this growing population.

With the growing array of treatment options for CLL patients, there is interest in determining what factors drive patient's choices about their treatment. A large multi-center study surveying over 1100 patients in 48 states asked patients about the resources they accessed prior to making their treatment decision and how influential each resource was. Seventy-nine percent of patients reported having seen a CLL expert (a provider focused on CLL at an academic/research center), and 95 percent of those rated the expert as extremely influential on their treatment decisions. Eighty-three percent of patients rated their own opinions as influential, and 59 percent rated the opinion of a general hematologist/oncologist as influential. Sixty-four percent were influenced by outside sources of information, such as family members, support groups, or online sources. Further, the majority of patients were offered more than one treatment choice by their provider, with the most important factors in selecting the treatment being response rate (91 percent), overall survival (88 percent), progression-free survival (86 percent) and long-term side effects (82 percent); cost and insurance coverage, though important to a majority of patients, lagged behind the top considerations at 66 percent. Patients

were also far more likely to accept potentially curable but high-risk treatments (such as cytotoxic chemotherapy and CART-cell immunotherapy) if no other options were made available to them. The researchers noted that this data could be used to enhance the informed consent process and provide more useful education on clinical trial opportunities, as well as more patient-centered care during the early days following diagnosis.

► *Contributors to this study included LRF SAB members and grantees Nancy Bartlett, MD of Washington University in St. Louis, and John Timmerman, MD of the University of California, Los Angeles.*

Laboratory Research

Before new therapies or treatment strategies can reach patients in a clinical trial, they must first be identified and tested in a laboratory setting. Many of this year's laboratory and translational research highlights included significant contributions from LRF grantees.

Graft-versus-host-disease (GVHD) is a serious complication that can occur after allogeneic stem cell transplant, a common treatment for several types of lymphoma. An international study at four transplant centers in the U.S., Germany, and Japan investigated whether the intestinal microbiota enterococcus could trigger the development of GVHD. Studying both pre-clinical mouse transplant models as well as stool samples from 1240 transplant patients, researchers discovered that patients whose intestinal microbiota was more than 30 percent enterococcus were at significantly increased risk for acute GVHD. In the mouse models, mice that developed GVHD saw a different strain of enterococcus bloom around seven days following transplant. Further labo-

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ratory tests found that mice who ate a lactose-free diet saw a significant decrease in the enterococcus bloom and were less likely to have lethal GVHD. Researchers suggested that given the similar relationship between enterococcus and GVHD in both mouse and humans, a lactose-free diet may similarly prevent enterococcus growth and lessen GVHD's impact on human patients. Yusuke Shono, MD of Memorial Sloan Kettering Cancer Center, an LRF grantee for a separate project on GVHD, contributed to this study.

LRF Postdoctoral Fellowship Grant recipient Samantha L. Kendrick, PhD of University of Arkansas for Medical Sciences contributed to a poster identifying a new class of molecular targets for inhibiting the B-cell receptor (BCR) signaling pathway in DLBCL. BCR has been identified as a key pathway which contributes to the growth of activated B-cell-like (ABC) DLBCL, however BCR inhibitors thus far have not achieved sustained or complete responses due to inherent resistance from mutations elsewhere in the BCR pathway. Dr. Kendrick and her collaborators hypothesized that the emerging field of DNA secondary structures (the study of structures formed by DNA pairings outside of the double helix) suggests that structures formed from the protein guanine (G), called G-quadruplex (G4) act as transcription switches that can turn gene expression on or off, thus targeting G4s will help avoid the mutations that cause cells to resist other targeted therapies by limiting the gene's ability to activate those mutations. Using a high throughput screening assay, the researchers demonstrated that all four BCR-related genes contain G4 structures

and identified seven G4 targeting compounds that interacted with at least one of these structures. The researchers concluded that DNA G4 is a new class of molecular targets for inhibiting BCR, and that further preclinical investigation of the seven compounds identified in their study is ongoing.

MCL Consortium member Xiaohong Zhao, MD, PhD of Moffitt Cancer Center, presented a poster in collaboration with senior author Jianguo Tao, MD, PhD, recipient of a 2018 LRF MCL Therapeutic Studies Grant. Many MCL patients develop resistance to the drug ibrutinib; patients who relapse after ibrutinib treatment experience disease progression and survival outcomes of less than a year. Drs. Zhao and Tao and their collaborators have modeled acquired resistance to ibrutinib in MCL and demonstrated that MCL cells become resistant to ibrutinib due to a mechanism that reprograms several crucial signaling pathways (kinases) in MCL cells with increased levels of Myc, a protein known to contribute to MCL cell growth. The researchers hypothesized that this adaptive mechanism indicates that, rather than creating therapies which target individual kinase pathways, the entire kinome, or the complete set of protein kinases in a cell's genome, must be inhibited. The researchers have designed transcription activation based combination therapy to overcome drug resistance and hinder MCL progression that is being tested in laboratory and mouse models. Additionally, they have developed a drug screen assay for primary MCL cells to predict drug responses of individual MCL patients and tailor a personalized therapeutic strategy. Translational studies of the therapy and the assay are forthcoming.

► This study also included contributions from LRF SAB Member Eduardo Sotomayor, MD of George Washington Cancer Center, and MCL Consortium Member Bijal D. Shah, MD, of Moffitt Cancer Center.

Summary

The 2018 ASH Annual Meeting showcased the growing body of research results on promising novel therapies, encouraging results for several rare lymphoma subtypes and intriguing studies from the laboratory and health services research. Many of these developments were either supported by the Lymphoma Research Foundation or involved contributions from LRF Scientific Advisory Board members, research consortium members, and grantees, including several recipients of Foundation research grants.

"The Lymphoma Research Foundation is proud to support the researchers conducting innovative studies to improve outcomes for lymphoma and CLL patients," said Meghan Gutierrez, Chief Executive Officer of LRF. "It is exciting to see the variety of work presented by our SAB members, grantees, and other colleagues in the research community as we continue to pursue our mission to find a cure for this disease."

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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.

LRF Helpline

The Lymphoma Research Foundation (LRF) offers a variety of support services to lymphoma patients, survivors, and caregivers. These programs include the LRF Helpline, which provides information about lymphoma and its treatment options, as well as the Lymphoma Support Network for peer support and encouragement. Individuals touched by lymphoma can also learn about novel and emerging therapies through our Clinical Trials Information Service. As part of this program, LRF staff can conduct individualized lymphoma trial searches for patients to assist them in making important decisions about their care. For more information about the Clinical Trials Information Service or any of LRF's support services, please contact the LRF Helpline at 1-800-500-9976 or helpline@lymphoma.org, or visit lymphoma.org/learn/supportservices.



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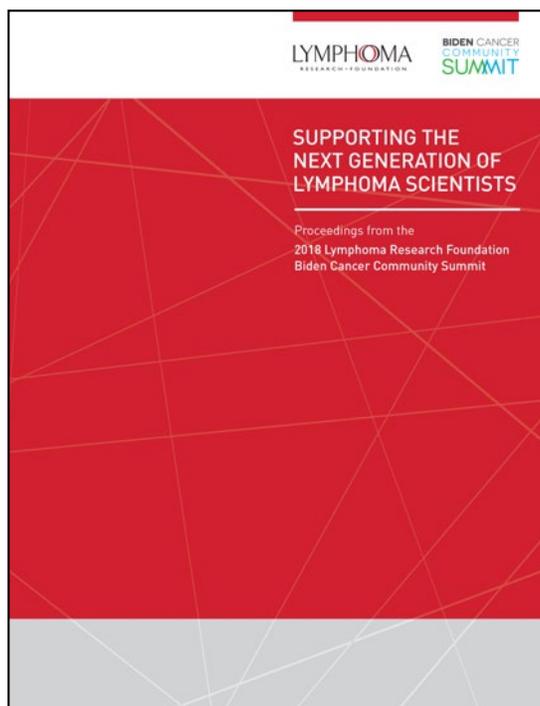
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Looking for information on clinical trials?

The Lymphoma Research Foundation (LRF) provides a free Clinical Trials Information Service. LRF's trained Helpline staff will conduct a search for potential trials based upon information provided by the patient.

Call the Helpline at (800) 500-9976 or email helpline@lymphoma.org



SUPPORTING THE NEXT GENERATION OF LYMPHOMA SCIENTISTS

A new monograph from the Lymphoma Research Foundation explores the challenges facing early career clinical and laboratory researchers in lymphoma and recommendations to diversify and strengthen the resources available to the next generation of lymphoma experts.

Now available on the LRF website.