LYMPHOMA RESEARCH • FOUNDATION

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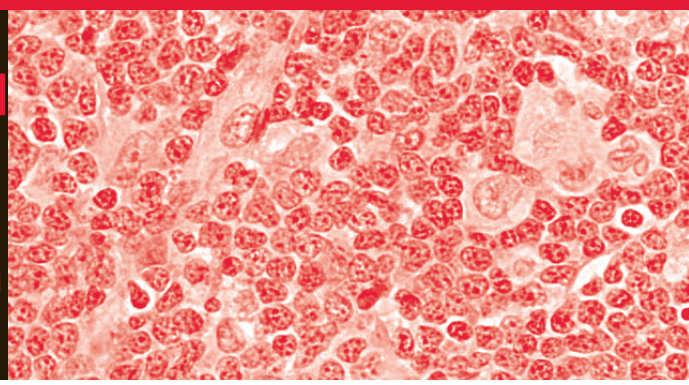
RESEARCH Report



ASH Annual Meeting Highlights Expanding and Improving Treatments for Lymphoma

44 of **45** current SAB members authored at least one abstract

Presenters at ASH included **69** investigators who have received an LRF grant

More than **20** abstracts included or proceeded from LRF-funded research

The Lymphoma Research Foundation at ASH 2015

The 57th American Society of Hematology (ASH) Annual Meeting and Exposition, held in Orlando, Florida in December, included a number of presentations highlighting the rapid advancement of treatment options for lymphoma patients, both in the development of new therapies and the refinement of existing treatment strategies. The ASH Annual Meeting provides a critical forum for leading hematologists/oncologists to present findings to over 20,000 of their peers, in what has become one of the leading scientific conferences for researchers across the hematologic malignancies, including those specializing in lymphoma and chronic lymphocytic leukemia (CLL). Lymphoma abstracts presented at the 2015 Annual Meeting covered a wide range of topics, with a number of significant study results in immunotherapies for both Hodgkin and non-Hodgkin lymphomas (NHL); the treatment and biology of CLL; targeted therapies in NHL, including some rare subtypes; and the growing importance of prognostic tools in refining treatment strategies. The Lymphoma Research Foundation (LRF) was proud to count a number of grantees, Scientific Advisory Board (SAB) members, and Mantle Cell Lymphoma Consortium members among the authors and presenters at this year's meeting. (See above for more on the contributions of LRF's grantees and scientific advisors.)

"The Lymphoma Research Foundation's commitment to advancing the field of lymphoma research through its investment in the most promising lymphoma research is highlighted through its breadth of reach at ASH," said SAB Chair Leo I. Gordon, MD, FACP, of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. "LRF continues to work with the best scientists in the field and invest in the research projects that have the greatest potential to impact and improve the treatment and understanding of lymphoma."

Immunotherapies Offer Promising New Avenue of Treatment

Immunotherapies are designed to boost the body's natural defenses to fight cancer. In 2015, several immunotherapies such as nivolumab (Opdivo) and pembrolizumab (Keytruda) received approval by the U.S. Food and Drug Administration (FDA) for melanoma, renal cell carcinoma, and small cell lung cancer. With trials of these therapies and others already underway in several

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FEATURED IN THIS ISSUE: Immunotherapy Response Criteria Workshop **Page 4**

The Lymphoma Research Foundation and the Cancer Research Institute convened a workshop to address the unique concerns of checkpoint inhibitors in lymphoma, under the chair of Bruce Cheson, MD, FACP, FAAAS, current member and past Chair of the Foundation's Scientific Advisory Board.

LETTER FROM THE CEO

Dear LRF Friends and Supporters,

The 57th Annual Meeting of the American Society of Hematology (ASH) unfolded over five days in early December in Orlando, Florida. This meeting and exposition is considered to be the world's premier event in hematology; it is 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.

I had the opportunity to attend this year's meeting and found it to be both instructive and illuminating. A number of significant studies in lymphoma research were presented by nearly 70 Lymphoma Research Foundation grantees and 44 of 45 Scientific Advisory Board members, including over 20 presentations related to Foundation-funded research. Key themes of this year's lymphoma research included the continued development of immunotherapy treatments, new targeted agents across a variety of subtypes, and several key studies expanding our understanding of chronic lymphocytic leukemia and its response to treatment.

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

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types of hematologic malignancies, the 2015 ASH Annual Meeting offered a number of updates on the possibilities of immunotherapies for lymphoma. Abstracts largely focused on two types of immunotherapy: immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cells.

In recognition of the unique concerns these therapies present for patients, LRF is developing an immuno-oncology fact sheet and other supportive educational resources, including special symposium at the 2016 North American Educational Forum on Lymphoma. In November 2015, LRF also convened a scientific workshop on checkpoint inhibitors, see page 4 for a summary of this event.

Checkpoint Inhibitors

Immune checkpoint inhibitors function by targeting a protein that occurs as part of a human immune cell. In the case of nivolumab and pembrolizumab, this protein is the programmed cell death protein 1 (PD-1). When PD-1 occurs on a tumor cell, it can help tumors escape destruction by the immune system; PD-1 inhibitors seek to attach to tumor cells and prevent the PD-1 pathway from functioning, allowing the immune system to destroy the malignant cells normally. At the 2014 ASH meeting, early promising data on PD-1 inhibitors for relapsed or refractory Hodgkin lymphoma were presented, including significant results from a phase I nivolumab trial on which LRF SAB members Stephen Ansell, MD, PhD of Mayo Clinic and Margaret Shipp, MD of Dana-Farber Cancer Institute, were key contributors. For the 2015 meeting, Dr. Ansell presented updated follow-up data from that study, which sought to

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understand whether the 87 percent overall response rate experienced by the study's 23 patients was durable (inducing a response of significant length), the necessary duration of treatment to receive a response, and whether retreatment was feasible. Patients in the study who completed the full course of treatment were followed for an additional year, with a possibility of retreatment if their disease progressed within that year. Of the 20 patients who responded in the initial results, ten (50 percent) have maintained durable responses, including two who have reached 40 weeks since their last treatment. Of the remaining ten patients, four (20 percent) eventually had their disease progress, with five (25 percent) reaching a response within 16 weeks and choosing to discontinue nivolumab to undergo stem cell transplant once they reached remission.

The research team, which also included Philippe Armand, MD, PhD of Dana-Farber Cancer Institute, a steering committee member for LRF's recent workshop on immunotherapies, concluded that nivolumab remained an effective therapy for relapsed/refractory Hodgkin lymphoma, with a durable response that could last for more than one year on its own, or allow a patient to progress to stem cell transplant. Three patients discontinued treatment due to adverse events (side effects), but researchers found that the incidence of immune-related adverse events did not increase with time on treatment, an indication that the therapy is well tolerated in most patients.

Hodgkin lymphoma was also the focus of a study combining ipilimumab (Yervoy), another checkpoint inhibitor, with brentuximab vedotin (Adcetris), the first such combination therapy to be reported. Presented by Catherine Diefenbach, MD, of New York University, a 2014 LRF Career Development Award recipient, the study followed 19 patients with relapsed or refractory Hodgkin lymphoma, four patients (33 percent) who had received prior brentuximab vedotin as a single therapy, and seven (67 percent) of whom had undergone stem cell transplant. Of the 12 patients who could be evaluated, the overall response rate was 67 percent, with five patients (42 percent) achieving a complete response. An additional two patients had stable disease (no further progression), suggesting this combination therapy may be more effective compared to brentuximab vedotin alone. The researchers further noted that more than half of the complete remissions reported occurred on a low dose of 1 mg ipilimumab, suggesting low doses (and thus less toxicity risk) may be effective for many patients. The study is continuing, with a later cohort testing a combination of brentuximab vedotin and nivolumab.

"LRF's commitment to advancing the field of lymphoma research is highlighted through its breadth of reach at ASH"

- Leo I. Gordon, MD, FACP

➤ *Researchers on this study included LRF SAB members Ranjana Advani, MD, of Stanford University, Stephen Ansell, MD, and Brad Kahl, MD of Washington University, St. Louis, as well as 2014 LRF Scholar Jonathon Cohen, MD, of Emory University.*

Primary mediastinal b-cell lymphoma (PMBCL) is another subtype in which PD-1 inhibition may be effective. The KEYNOTE-013 study, which tests pembrolizumab in patients with a variety of relapsed/refractory hematologic malignancies, reported the preliminary results of its PMBCL cohort, including contributions from SAB member Margaret Shipp and Philippe Armand. With ten patients enrolled through July 2015, nine evaluable patients achieved an overall response rate of 44 percent (four patients), with one patient achieving complete response. All four responses were still active at the time the data was reported. The researchers noted that no patient discontinued for toxicity, suggesting a well tolerated therapy, and that the generally poor outcome of PMBCL patients on standard therapies suggests further studies of pembrolizumab on this population are needed. KEYNOTE-013 is still enrolling in several locations across the U.S., Canada, and Europe.

CAR T-Cells

Chimeric antigen receptor (CAR) T-cells, another class of immunotherapy, were also featured in several prominent abstracts at ASH. Unlike standard therapies, CAR T-cells use actual human immune cells, which are removed from a patient (or in some cases sourced from a donor), modified with the chimeric antigen receptor to recognize genetic receptors specific to the patient's form of cancer, and reintroduced to the patient. LRF is proud to have provided funding for several early studies in CAR T-cells for lymphoma; at the 2015 ASH meeting, two recent LRF grantees in CAR T-cells presented important data on this topic.

Mariusz Wasik, MD of the University of Pennsylvania, received a 2013

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Lymphoma Research Foundation, Cancer Research Institute Convene Workshop in Immunotherapy Response Criteria

On November 20, 2015, the Lymphoma Research Foundation, in partnership with the Cancer Immunotherapy Consortium of the Cancer Research Institute (CRI), convened a unique and timely workshop "Immunotherapy Response Criteria for Hematologic Malignancies" in Washington, D.C. The workshop allowed leading clinician-scientists, federal regulators, and pharmaceutical researchers to share their experience with immune checkpoint inhibitors and other agents to address issues of patient response unique to this class of therapies.

PD-1 inhibitors are a rapidly growing class of immunotherapy for several cancers, including lymphoma (see our ASH update on page 2). Recent research has suggested that patients given these therapies, may experience a phenomenon called a "flare" or "pseudo-progression," where patients initially appear to experience disease progression before eventually demonstrating a response to the therapy. Current standards for measuring disease response and progression in lymphoma rely heavily on CT scans and PET imaging, with which a flare could be misinterpreted as progressive disease: with growth of previous lesions or development of new lesions which are bright on a PET scan. Misinterpretation of the scans could result in removal of a patient from a therapy before deriving full benefit, in addition to causing immunotherapy clinical trials to undercount the number of patients showing a response.

In convening the November workshop, LRF and CRI brought together academic and pharmaceutical industry researchers as well as representatives from government regulatory agencies to address the flare phenomenon and discuss how standard treatment response criteria could be adjusted to better account for this reaction in hematologic malignancies. Central to the workshop discussion was the immune-related Response Criteria (irRC), an existing protocol for evaluating solid tumors' (such as those found in lung and breast cancer) responses to immunotherapy. Developed in 2009 by CRI Scientific Advisory Council members Jedd Wolchok, MD, PhD, and Axel Hoos, MD, PhD (a presenter at the workshop), the irRC model enables clinicians to better characterize patient response to immunotherapy regardless of any flare effects. However, there is less experience with flare reactions in patients with lymphoma, and the solid tumor criteria cannot be directly translated to lymphomas. Thus, modifications to the lymphoma response criteria are needed. Workshop attendees discussed potential adjustments to the current lymphoma criteria, with the focus on a development of standards for evaluating patients: when patient samples should be analyzed, what markers should be used to form conclusions, and how those conclusions should influence decisions regarding further treatment. Marc Theoret, MD, of the U.S. Food and Drug Administration (FDA) assisted the discussion with commentary on how use of the irRC impacted the FDA's evaluation of immunotherapies in solid tumors.

Bruce Cheson, MD, FACP, FAAAS, of Lombardi Cancer Center at Georgetown University, chaired the November 2015 workshop.

Investigators involved in clinical trials with checkpoint inhibitors in lymphoma presented case studies which demonstrated the problem. Lawrence H. Schwartz, MD, of Columbia University Medical Center provided a special presentation on the use of imaging in evaluating response in hematologic malignancies. Participants acknowledged that a better understanding of lymphoma immunology in conjunction with improved methods to assess response to treatment will enhance our ability to improve the care of patients treated with novel, targeted agents.

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Mantle Cell Lymphoma Exploratory/ Developmental Grant from LRF to perform pre-clinical research on CAR T-cells in MCL. At ASH, Dr. Wasik served as senior author on results of a trial testing an ibrutinib (Imbruvica) and CAR T-cell combination therapy on MCL cells in a laboratory setting. The researchers developed a mice model for MCL and tested a CAR T-cell designed to target the CD19 protein expressed by MCL B-cells (CART19) in combination with ibrutinib as well as with CART19 and ibrutinib alone. The researchers found a significant improvement in tumor control compared to mice treated with single agents, and noted that mice treated with the combination therapy had higher numbers of circulating CART19 cells than those treated with CART19 alone, suggesting an ibrutinib + CAR-T combination could be an effective strategy in patients with MCL or other types of B-cell lymphoma.

With excitement over the potential of this therapy growing, 2015 Career Development Award (CDA) recipient Rayne Rouce, MD of Baylor University, presented a poster investigating the important issue of safety for patients who receive multiple doses of CAR T cells. Dr. Rouce, who received her CDA for a separate study in CAR T-cells, worked with colleagues to perform a retrospective review of 47 patients who received more than one dose of CAR T-cells at Baylor from 2009 through 2014, identifying 13 patients who experienced a serious adverse event or toxicity in a subsequent CAR T-cell infusion. They found that the majority of patients who experienced severe adverse events were experiencing hematologic or electrolyte abnormalities that resolved without intervention, with only three patients experiencing adverse events possibly attributable to their CAR T-cell infusion. Though Dr. Rouce and her colleagues noted that evaluation of a larger cohort is needed, particularly to determine whether the timing of multiple infusions could be contributing to the severe adverse effects, their current findings suggest multiple doses of CAR T-cells do not cause a severe issue for most patients.

A study including contributions from SAB member Andre Goy, MD, of Jon Theurer Cancer Center, investigated CAR T-cells potential as a treatment for the B-cell malignancies that occur after allogeneic hematopoietic stem cell transplantation. These malignancies, the leading cause of death after stem cell transplantation, are generally treated with infusions of donor lymphocytes from the transplant donor, which can often cause graft-versus-host disease (GVHD). The researchers treated 20 patients who developed a wide range of B cell malignancies after transplant with CAR T-cells developed from their donor's cells. Eight of these patients obtained remission, with six complete remissions. Although most effective in acute lymphoblastic leukemia (ALL), patients with chronic lymphocytic leukemia (CLL) and other B-cell lymphomas also saw response, with one CLL patient reporting an ongoing CR of more than 30 months. Moreover, no patients developed GVHD following treatment, suggesting CAR T-cells may be a safer and more effective treatment for post-transplant malignancies.

The ZUMA-1 study, an ongoing study of KTE-C19, a CAR T-cell therapy, also presented encouraging results in non-Hodgkin lymphoma (NHL), including contributions from SAB member Nancy Bartlett, MD of Washington University in St. Louis. The preliminary results included data from seven subjects with aggressive NHL that did not respond to prior treatments. Five patients (71 percent) experienced a response to therapy, with four complete remissions, which were observed one month after therapy and still ongoing after three months. Though still early in the study, ZUMA-1 is particularly interesting as a multi-center study conducted at major cancer centers that do not specialize in CAR T-cell therapy; an important test of whether this class of immunotherapy can be effective if widely available. Shortly following the ASH Annual Meeting, the FDA announced KTE-C19 was receiving breakthrough therapy designation, allowing it to enter an accelerated approval process.

CLL: Biology and Treatment

Chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) was a much discussed subtype at the 2015 ASH Annual Meeting, following the presentation of several abstracts featuring significant results in both improved response to treatment and understanding the biology of this subtype.

CLL and Targeted Agents

Researchers continue to develop their understanding of ibrutinib's (Imbruvica) impact on CLL. A comparative analysis study featuring contributions from MCL Consortium member Simon Rule, MD of Derriford Hospital in the United Kingdom, performed an indirect comparison of the RESONATE trial (which demonstrated single agent ibrutinib's effectiveness in relapsed/refractory CLL) and the HELIOS trial (which demonstrated the effectiveness of ibrutinib combined with the bendamustine and rituximab (BR) regimen in a similar patient

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population). Although researchers found some evidence to suggest that the combination therapy does not improve progression free survival or overall survival compared to ibrutinib alone, they noted that since follow up in both trials is still ongoing, future analysis is needed to confirm these conclusions.

Additionally, the RESONATE-2 trial explored the possibility of ibrutinib versus chlorambucil as a first line treatment in CLL patients over 65 years of age. The international, multi-center trial results, including contributions from SAB member Nancy Bartlett, MD, of Washington University in St. Louis and Career Development Award recipient Paul M. Barr, MD of the University of Rochester enrolled 269 patients, finding that the progression free survival rate was 89.9 percent with ibrutinib, compared to 51.5 percent for chlorambucil. In addition, ibrutinib had a significantly higher overall response rate of 86 percent (compared to 35 percent) and patients were significantly less likely to discontinue treatment because of adverse events (9 percent versus 23 percent). This trial's results have been used as the basis of an application to the FDA for approval of ibrutinib as a first line treatment for older patients with CLL.

Idelalisib's (Zydelig) effectiveness in CLL was also strengthened by data presented at ASH. Already an FDA approved treatment combined with rituximab in relapsed/refractory CLL, a large scale study investigating the effects of idelalisib added to the bendamustine and rituximab (BR) regimen was presented by SAB member Andrew Zelenetz, MD, PhD of Memorial Sloan Kettering Cancer Center, who was also first author. The study enrolled 416 patients who were given either idelalisib plus BR or a placebo with BR. The results indicated that the idelalisib arm experienced longer progression free survival (23 months versus 11 months), with median overall survival not yet reached for either arm.

In a separate study, researchers including 2005 Career Development Award recipient Jennifer Brown, MD, PhD of Dana-Farber Cancer Institute, examined the toxicity of idelalisib plus ofatumumab as a first line CLL therapy. The researchers noted an increase in both the frequency and severity of toxicities and adverse events on the 21 patients enrolled in the study compared to established rates for relapsed/refractory CLL patients. However, patients who experienced adverse events possessed different levels of certain biomarkers on their regulatory T-cells (Tregs) than those unaffected, suggesting that these biomarkers could be used to identify the patients that will be best able to tolerate idelalisib as a front line therapy.

Understanding CLL Biology

Two abstracts – featuring work by three recent LRF grantees – discussed the biology of CLL in hopes of better understanding both why it forms and how to combat its resistance to therapy. Lili Wang, MD, PhD, of Dana-Farber Cancer Center, a 2013 Postdoctoral Fellowship recipient, presented research on the role of the protein SF3B1, which influences the splicing of RNA within cells. Dr. Wang and her colleagues, including senior author Catherine Wu, MD, also of Dana-Farber, who received a 2012 CLL Collaborative Grant, also to study SF3B1, attempted to learn the protein's exact role in the pathogenesis of CLL by creating a specialized mouse model to study the specific mutation of SF3B1 thought to lead to CLL and investigating how this mutation affects B cell development and function. Researchers also noted a significant increase in B cells in their mouse model, suggesting that mutated SF3B1 introduces a defect into normal B cells causing an increase in the number of cells. However, this mutation alone did not lead to an increase in the CD5 + CD19+ cells known to lead specifically to CLL, suggesting SF3B1 must combine with other mutations to generate CLL.

Sean M. Post, PhD, of MD Anderson Cancer Center, also a 2012 CLL Collaborative Grant recipient, was senior author on a poster of the project partially funded by his LRF grant, which investigated the impact of p53 mutations on CLL's resistance to treatment. TP53, a tumor suppressor protein, is part of the crucial chromosome 17 region of human B-cells – patients with 17 p deletion are considered at greater risk for refractory disease than other CLL patients. With previous research demonstrating that mutant p53 is often present in cells that expand, rather than respond, to treatment, Dr. Post and his colleagues investigated whether ibrutinib affected p53 mutations in CLL patients, which could impede their response to treatment. Using a mouse model, the researchers demonstrated that in CLL with and without a TP53 mutation, ibrutinib significantly extended survival and reduced CLL cells; further analyses of tumor samples revealed that ibrutinib impacted the BTK and other pathways as designed regardless of p53 mutational status. Dr. Post's research, begun prior to the FDA's July 2014 approval of ibrutinib for CLL patients with 17p deletion, provides evidence of the biologic mechanism that makes the

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therapy an important advance for this group of CLL patients.

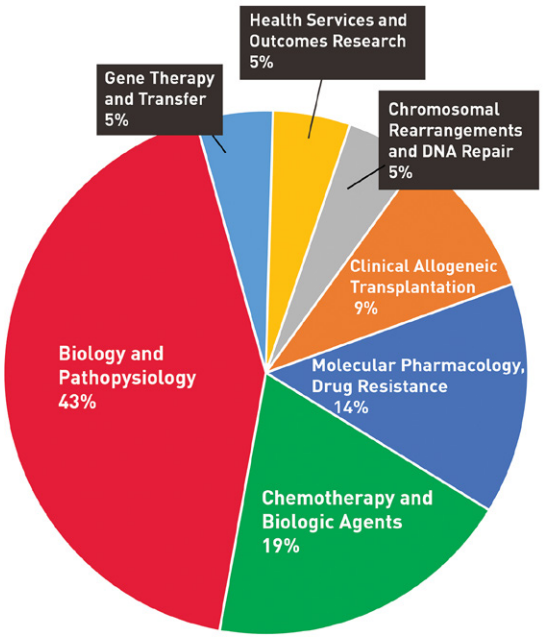
New Targeted Therapies in NHL

The expansion of treatment options in lymphoma experienced with the FDA approval of ibrutinib, rituximab, and other targeted therapies is likely to continue over the next several years, with a number of abstracts at the ASH Annual Meeting presenting significant results of either new novel agents or testing existing agents in new subtypes.

New Inhibitors

Two significant European studies presented encouraging results for two new agents being tested in non-Hodgkin lymphoma (NHL). MCL Consortium Executive Committee member Martin Dreyling, MD, PhD of the University of Munich-Grosshadern, was a contributor to an abstract reporting results for the MCL cohort of a trial of copanlisib across NHL. Copanlisib, a PI3K inhibitor, targets both the PI3K-α and PI3K-δ subclasses of this protein, where similar drugs like focus on PI3K-δ alone. Researchers reported that 11 MCL patients with relapsed or refractory disease demonstrated an overall response rate of 64 percent (seven patients), with two patients achieving complete response. Additionally, a median duration of response of 150 days, with one third of patients achieving at least 270 days of response, suggests the viability of copanlisib as a treatment for relapsed MCL, with a larger trial for ibrutinib-pretreated MCL patients already underway.

A French study of the first in-human results for tazemetostat, were presented by Vincent Ribrag, MD, of the Institut Gustave Roussy (Villejuif, France). Tazemetostat is an oral inhibitor for EZH2, a protein which has been previously found to be a significant contributor to the growth of several forms of NHL. 15 relapsed/refractory NHL patients were evaluable, with objective responses occurring in five of nine diffuse large B-cell lymphoma (DLBCL) patients, three of five follicular lymphoma (FL) patients, and the sole marginal zone lymphoma (MZL) patient. Duration of responses lasted up to 19 months, with four patients' responses still ongoing. A larger scale trial of tazemetostat is currently underway.



ASH abstracts related to Lymphoma Research Foundation grants were distributed over several research focus areas.

Existing Therapies in New Subtypes

Bortezomib (Velcade), already approved in MCL, is being tested in combination with R-CHOP (creating VR-CHOP) in non germinal center (GCB) DLBCL as part of the Pyramid Trial. SAB member John Leonard, MD, of Weill Cornell Medical College, presented the study, which tested R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) versus VR-CHOP in adults with previously untreated non-GCB DLBCL, a subtype with less favorable prognosis than other DLBCL subgroups. The study included 183 patients treated at 69 sites but found no significant advantage for VR-CHOP vs R-CHOP (for example, 2-year progression free survival was 77 percent for R-CHOP versus 82 percent for VR-CHOP). The researchers noted that the R-CHOP patients had better outcomes and a lower event rate than expected, which may indicate that the patients selected happened to be among those who respond well to R-CHOP alone. However, Dr. Leonard noted that these results have important implications for upcoming studies that target subsets based on cell of origin.

➤ *This study also included contributions from SAB members Christopher Flowers, MD of Emory University, Sven de Vos, MD, PhD of UCLA, and MCL Consortium member Ian Flinn, MD, PhD of Sarah Cannon Research Institute.*

Bendamustine is under further investigation not just as a combination therapy in CLL, but, in separate studies, for its potential in Hodgkin lymphoma and MCL. The MCL study investigated how a bendamustine and rituximab combination compared to R-HCVAD (rituximab plus a standard chemotherapy regimen) in preparing MCL patients for autologous stem cell transplant. Researchers accrued 53 patients to the study and closed the study early due to stem cell mobilization failures in the R-HCVAD arm. However, 13 of the 21 patients in the R-B arm achieved minimal residual disease (MRD) negative status by the end of their RB treatment; all 13 patients were in an

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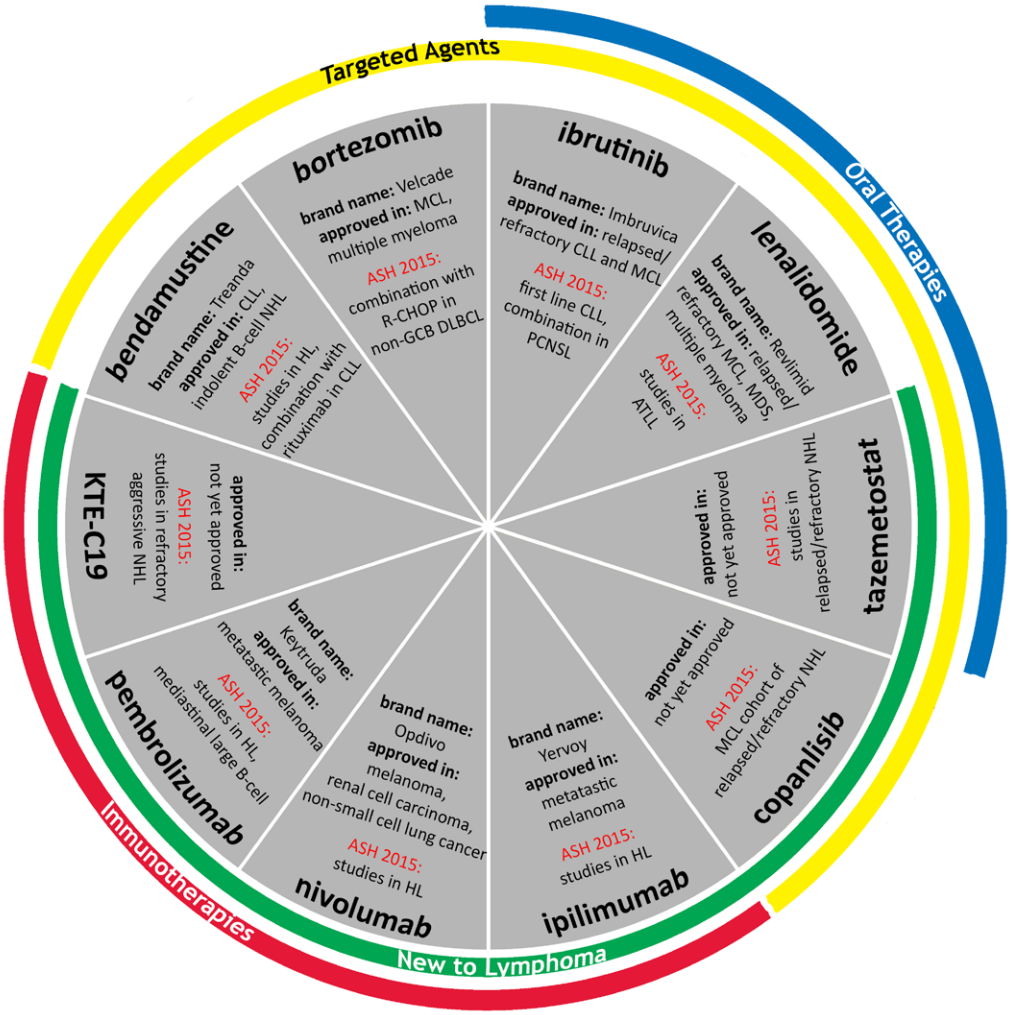

A comparison of several therapies which reported results at the ASH Annual Meeting in indications not yet approved by the U.S. Food and Drug Administration.

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ongoing remission, including three who did not end up undergoing a transplant.

➤ *This study included contributions from LRF SAB members Jonathan Friedberg, MD, MMSc of the University of Rochester (senior author), Bruce Cheson, MD, FACP, FAAAS of Georgetown University , Kristie Blum, MD of Ohio State University, Brad Kahl, MD of Washington University in St. Louis, Sonali Smith, MD of the University of Chicago, and 2012 Career Development Award recipient Paul Barr, MD, also of Rochester.*

In Hodgkin lymphoma, patients older than 60 have poorer outcomes than younger patients, with less tolerance for the standard chemotherapy regimens. Researchers including SAB member Jonathan Friedberg, MD, MMSc, compared brentuximab vedotin (BV) alone with combination therapies of BV with either bendamustine or dacarbazine (DTIC). Though the study is ongoing, the 21 patients treated thus far with the DTIC combo had achieved an overall response rate of 100 percent, with 62 percent complete remissions; overall response in the first nine patients receiving the bendamustine combo was also 100 percent (with 78 percent complete remissions), although researchers noted they had limited observation time with that cohort, and that future patients on the study will receive lower doses to improve tolerability. With 70 percent of the trial's patients considered ineligible for chemotherapy, the promising responses suggest new treatment possibilities for an often overlooked population of Hodgkin lymphoma patients.

Therapies for Rare Subtypes

Patients with rare subtypes were not left out of the new therapy pipeline. For patients with relapsed adult T-cell leukemia-lymphoma (ATLL), a Japanese study presented by Hiroshi Fujiwara, MD, PhD of Ehime University Hospital tested the efficacy of single agent lenalidomide. Of the 26 patients tested, the overall response rate was 42 percent (11 patients). Five patients achieved complete response, with responses seen across acute, lymphoma, and unfavorable chronic type ATLL. Though particularly important in Japan, where ATLL is more common than the rest of the world, these results suggest lenalidomide may be a viable treatment option for this subtype.

In marginal zone lymphoma (MZL), a study of idelalisib as a monotherapy proved promising for relapsed or refractory MZL patients. The presentation focused on two single arm studies using idelalisib in varying doses. One study reported only one of six patients with progressive disease, with the other five reporting a partial response to treatment. The other arm reported an overall response rate of 47 percent (seven of 15 patients), including one complete response. Responses were recorded in MZL patients across all three types: splenic (SMZL), nodal (NMZL), and mucosa-associated lymphoid tissue (MALT). The median progression free survival was six to seven months in both studies,

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although follow-up was ongoing. The researchers noted that though working with a small patient population, idelalisib appears to be an option for MZL patients and that larger scale trials of idelalisib across indolent NHL may be open to this group.

➤*Researchers on this study included SAB member Sven de Vos, MD PhD of UCLA and MCL Consortium Member Ajay Gopal, MD of the University of Washington (a multiple LRF grantee in MCL).*

The National Cancer Institute presented results of a study on primary central nervous system lymphoma (PCNSL) a rare type of DLBCL, incorporating ibrutinib into a regimen called DA-TEDDI-R (temozolomide, etoposide, doxorubicin, dexamethasone, ibrutinib and rituximab with intraventricular cytarabine), which is designed to penetrate the blood in the central nervous system (CNS), a particular challenge for PCNSL treatments. Both untreated and relapsed/refractory patients were eligible for this study. Eleven patients have enrolled in the ongoing study, with eight patients being evaluable by ASH. Seven of the eight patients achieved partial response with one mixed response after the ibrutinib portion of the treatment alone, with researchers performing biopsies to determine that ibrutinib is able to successfully penetrate the CNS. Five patients continued on to receive DA-TEDDI-R; all five achieved complete remission, with four remissions ongoing (one response at more than six months), and one relapse after three months. Accrual on this trial is still ongoing.

➤*Researchers included LRF SAB members Kieron Dunleavy, MD, Louis M Staudt, MD, PhD, and 2014 LRF Scholar Catherine Lai, MD, all of the National Cancer Institute.*

Prognostic Tools and Epidemiology

Although the development of new therapies for lymphoma patients was a large part of the discussion at the ASH Annual Meeting, several significant abstracts demonstrated how treatment strategies and patient outcomes can be improved through prognostic tools, imaging, and even a patient's choice of treatment facility.

Ronald Go, MD, of the Mayo Clinic, presented a study using the National Cancer Data Base (NCDB) to determine whether the volume of NHL patients treated at a facility affects the overall survival rate of those patients. Because the NCDB covers 70 percent of the cancer population in the United States, the researchers were able to compare data from over 278,000 NHL patients cared for at over 1,100 facilities from 1998 to 2006. Patients treated at facilities that treated a mean of 33 or more NHL patients a year had an overall survival of 83.6 months, with a corresponding decrease in length of overall survival as the number of patients per year decreased – facilities treating 13 or less patients a year had an overall survival of 61.8 months. This study, the first in the United States to use a national sample to demonstrate the relationship between facility volume and outcome, indicates the importance of patient access to facilities experienced in treating NHL.

The use of imaging as a prognostic tool was addressed in several abstracts at ASH. Researchers on a multi-center study tested the use of positron-emission tomography (PET) following one to three cycles of ABVD chemotherapy in Hodgkin Lymphoma, intensifying treatment for patients with positive PET scans (showing disease progression). Of 144 patients studied, 13 were PET+ after their initial cycles and had their treatment escalated, eight of the PET negative patients relapsed (six percent), while four of the PET positive group relapsed (31 percent). Researchers noted the interim PET scans were an excellent indicator of the likelihood of relapse, however, the more intense treatment given to the PET positive patients failed to improve their three-year progression free survival rate from 66 percent to match the 85 percent PFS of the PET negative group, indicating that new treatment options are still needed for this group.

➤*Researchers on this study included LRF SAB members Nancy Bartlett, MD, Bruce Cheson, MD, Jonathan Friedberg, MD, MMSc, Eric Hsi, MD, of Cleveland Clinic, Brad Kahl, MD, FACP, FAAAS, and John Leonard, MD.*

A study involving hospitals in Denmark, Canada, the United Kingdom, and Australia investigated the use of PET-CT staging of DLBCL patients at their initial diagnosis to predict central nervous system relapse following treatment with R-CHOP or similar regimens. Researchers including LRF SAB member Laurie Sehn, MD, of the British Columbia Cancer Agency (BCCA), studied more than 1500 patient records, finding that patients with an initial PET-CT that identified three or more extranodal sites of involvement had a significantly higher risk of developing CNS relapse. Patients with three sites had a hazard ratio of 6.3, more than double the risk for two sites (2.8); four or more sites had a hazard ratio of 17.2. The researchers added that this higher risk population could benefit from further biomarker studies to identify more effective therapies.

Risk stratification is a crucial part of follicular lymphoma treatment,

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as some patients will remain stable for years without treatment, while others will have a faster-progressing, and more aggressive, disease. The risk model m7-FLIPI is composed of seven biomarkers, the FL International Prognostic Index (FLIPI), and the Eastern Cooperative Oncology Group (ECOG) performance status, with the goal of improving risk stratification for patients with FL receiving first line immunochemotherapy (such as R-CHOP). Researchers tested the efficacy of the m7-FLIPI model on patient data from two cohorts, 151 patients from a German study and 107 patients from a BCCA registry. The researchers found that though most of the patients classified as high-risk did see disease progression in 24 months or less, approximately half of the patients with rapid disease progression were classified as low-risk. The researchers concluded that further refinement of the m7-FLIPI was needed, with the goal of more accurately identifying high risk cases that could benefit from the innovative first-line approaches being developed.

➤ *Researchers on this study included SAB Members Stephen Ansell, MD, Jonathan Friedberg, MD, MMSc, Randy Gascoyne, MD of the BCCA , Laurie Sehn, MD, and MCL Consortium Executive Committee member Martin Dreyling, MD, PhD.*

Summary

The 57th ASH Annual Meeting and Exposition once again illustrated the exciting developments in current lymphoma research, whether through promising new therapies or new ways of identifying the most effective treatments for lymphoma patients. Though a number of significant studies in CLL were presented at the 2015 meeting, exciting results were presented across a wide variety of subtypes, including some rare lymphomas and high-risk patient groups. Though targeted therapies remain an effective option for a growing number of lymphoma patients, immunotherapies such as checkpoint inhibitors and CAR T-cells are increasingly demonstrating significant results in clinical trials. Researchers also continue to investigate ways to improve patient treatment, whether through prognostic tools designed to direct patients to the most effective therapy, considerations of patient safety, or better understanding of the biologic mechanisms of lymphoma.

A number of LRF grantees, Scientific Advisory Board members, and MCL Consortium members contributed to this year's ASH Annual Meeting, including several recipients of LRF's Young Investigator grants – Clinical Investigator Career Development Awards, Postdoctoral Fellowship, and the LRF Scholars, who participate in the Lymphoma Clinical Research Mentoring Program – demonstrating the effectiveness of LRF's commitment to supporting early career researchers.

"The 2015 ASH Annual Meeting demonstrates the variety of exciting research happening in lymphoma today," said Meghan Gutierrez, LRF Chief Executive Officer. "The Lymphoma Research Foundation is proud to have worked with a number of the leading lymphoma experts, researchers, and clinicians, including those early in their career, who presented at the 2015 meeting. The Foundation remains committed to supporting researchers and projects that are not only at the forefront of research, but have the greatest potential to improve patient care and treatment options."

Response Criteria Workshop

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At the conclusion of the workshop, participants discussed next steps, including the production of an initial document based on the workshop discussion, with a potential follow up document as current immunotherapy trials produce additional data. Participants also discussed the need for clinical trials that specifically investigate the flare phenomenon in lymphoma with more frequent scans and biopsies.

Workshop Chair Bruce Cheson, MD, FACP, FAAAS of Georgetown University, a long-time LRF Scientific Advisory Board (SAB) member and prior SAB Chair, noted that the workshop marked an important first step in a discussion that is only growing in importance for lymphoma patients. "With several clinical trials of immunotherapies in lymphoma already underway, it is crucial to develop standardized response criteria that take into account the unique effects these therapies can have on a standard scan or biopsy," Dr. Cheson said. "By convening the Immunotherapy Response Criteria Workshop, LRF and CRI have launched a discussion on this important issue that will ultimately lead to better assessment of, and thus better treatment for, lymphoma patients."

SCIENTIFIC ADVISORY BOARD

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

Laura and Michael Tepper of Chicago, Illinois have participated in the Chicago Lymphoma Walk since the very first Walk in 2003. At the 2015 Chicago Walk, their team, Laura's Loony Lymphomettes, raised over $100,000 for LRF's research program. A lymphoma survivor herself, Laura has also seen family members diagnosed with the disease; some, including herself, have benefited from treatments that weren't available when the Walk started. "I know there are a zillion good causes out there, but I have a personal connection to this one," Laura says. "The money raised for research through LRF leads to better treatments and will, hopefully, eventually lead to a cure." Having witnessed the Chicago Walk's growth from 300 participants the first year to over 1,000 in 2015, Laura plans to continue participating. "There is no better way to spend the day than with those you love, enjoying the beautiful lakefront and raising money for a great cause."

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IN THIS ISSUE:

Looking for updates on a specific lymphoma?

The Lymphoma Research Foundation (LRF) maintains six disease-specific websites which provide visitors with data on specific lymphoma subtypes, including diagnostic information, treatment options, and free patient and caregiver resources.

lymphoma.org/FocusOn

Want to learn more about lymphoma clinical trials?

CLINICAL TRIALS INFORMATION SERVICE

The Lymphoma Research Foundation (LRF) provides a Clinical Trials Information Service to increase awareness about investigational treatments for lymphoma being evaluated at cancer treatment centers nationwide. The specially-trained Helpline staff will conduct a search for potential lymphoma treatment trials based upon the medical information provided by the patient.

Patients are strongly encouraged to discuss with their physician the summaries provided by LRF. Your physician will be familiar with your medical history and can best evaluate all of the study criteria to determine if the clinical trial is appropriate.

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