



# Oral Therapies in Lymphoma: Opportunities and Challenges in Research and Treatment

A LYMPHOMA RESEARCH FOUNDATION WHITE PAPER

Dear Colleague:

On behalf of The Lymphoma Research Foundation, we are pleased to present this White Paper titled *Oral Therapies in Lymphoma: Opportunities and Challenges in Research and Treatment*. The Lymphoma Research Foundation is the nation's largest non-profit organization devoted exclusively to funding innovative lymphoma research and providing individuals with lymphoma and health care professionals with up-to-date information about this type of cancer. LRF's mission is to eradicate lymphoma and serve those touched by the disease.

In September 2015, the Foundation hosted the *Oral Therapies in Lymphoma Workshop* in Washington, D.C., as the first-ever multi-stakeholder collaborative workshop on this topic. The Lymphoma Research Foundation brought together scientists, clinicians, patients, the pharmaceutical and biotechnology industries, government, patient advocates, and others from the cancer community, to explore the changing nature of lymphoma and chronic lymphocytic leukemia (CLL) treatment, with a particular focus on the impact and implications of oral therapies.

The advent of effective oral therapies marks a significant change in the way patients receive treatment. Therefore, to ensure patients receive the right therapy at the right time, and achieve the best outcome, significant attention and response is required. As such, the discussion at the workshop, and the information and recommendations contained in this White Paper acknowledge the difference in the delivery of oral therapy from traditional infused chemotherapy and reflect the subsequent issues facing patients with lymphoma and CLL and their cancer care teams.

As the co-chairs of the workshop, we are proud of the work that has been done on this critically important topic and thank our colleagues who served as presenters and panelists at the meeting. We also wish to express our appreciation to all who attended and participated. The information that follows is comprehensive and robust because of the active engagement – and contributions – of so many individuals, organizations, and partners over the course of the Workshop.

The White Paper that follows outlines the key issues, opportunities, and challenges facing patients, the cancer care team, and the research community with respect to the development, accessibility, and delivery of oral agents to patients with lymphoma and other blood cancers. The Lymphoma Research Foundation presents this White Paper as its latest contribution to the ongoing discussion on the growing importance of the role of oral therapies in the treatment of cancer.

We hope you find the information useful to your work. We and The Lymphoma Research Foundation stand ready to work with you on issues of mutual interest and priority so together we can achieve advancements in the care and treatment – survival and quality of life – for individuals affected by lymphoma and CLL.

Sincerely,



Jonathan W. Friedberg, M.D., M.M.Sc



Michael E. Williams, M.D., ScM

## Introduction

Lymphoma and chronic lymphocytic leukemia (CLL) are a complex, heterogeneous group of malignancies traditionally managed by cytotoxic chemotherapy, immunotherapy, radiation treatment, and, in some cases, by high-dose chemotherapy and stem cell transplantation. According to the American Cancer Society, an estimated 80,900 people were newly diagnosed with lymphoma (Hodgkin and Non-Hodgkin) in 2015 and approximately 20,940 people lost their lives to the disease. The American Cancer Society estimates an additional 14,620 new cases of CLL each year, with the average age of onset at 71 and approximately 70 percent of patients needing therapy.<sup>1</sup>

Of particular significance for researchers, clinicians, Pharmaceutical industry, and government is that survival of lymphoma and CLL diseases is improving and patients are living longer with – or in remission from – their disease. Currently, in the United States, an estimated 761,659 people are living with – or in remission from – lymphoma and an additional 119,386 people are living with CLL. In total, approximately 880,000 people are living with – or in remission from – mature lymphoid malignancies.<sup>2</sup>

As the number of available agents for lymphoma and CLL patients has grown over the course of the past decade, oral cancer therapy is emerging as an important option for patients who can manage the prescribed regimens and recognize possible complications. Certain patients may select an oral treatment because of the appeal of prolonged remission; the perception that it is more convenient to administer; possible elimination of frequent office visits; and/or a greater sense of control over their own cancer care. With this shift in cancer care, scientists, clinicians, and patients have been paying greater attention to – and are engaged in ongoing discussions regarding – the efficacy, value, cost, and convenience of oral cancer therapy. Scientists and clinicians, in particular, have begun to explore how the changing nature of lymphoma and CLL treatment impacts patients in the long-run.

The anticipated development and expanded use of oral therapies over the next decade will have a profound impact on the future of lymphoma and CLL care and patient outcomes. To explore the opportunities and challenges associated with the advent and expansion of the availability and use of targeted oral anti-lymphoma agents, The Lymphoma Research Foundation hosted the *Oral Therapies in Lymphoma Workshop* in September 2015, which brought together scientists, clinicians, patient advocates, Pharmaceutical industry representatives, federal agency officials, and other stakeholders from the lymphoma and CLL community. The workshop was designed to set the agenda and inform key stakeholders of the current challenges in oral treatment for

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<sup>1</sup> *Cancer Facts and Figures 2015*. American Cancer Society; 2015.

<sup>2</sup> *Leukemia and Lymphoma Society: Facts 2014-2015*.  
(See also [https://www.lls.org/sites/default/files/file\\_assets/facts.pdf](https://www.lls.org/sites/default/files/file_assets/facts.pdf)).

lymphoma and CLL and to determine priority action items for further investigation and investment.

Specifically, the goal of the workshop was to discuss some of the very particular nuances related to oral therapeutics in hematologic malignancies and mature lymphoid malignancies and to develop a priority list of action items to inform clinical trials and patient care. To that end, throughout the Workshop, a number of key issues, themes, and recommendations emerged. These consensus areas of priority are outlined in this paper, including recommendations for next steps.

It is important to note there is significant disease heterogeneity under the larger umbrella of lymphoma; some lymphomas are acute, aggressive, and immediately life-threatening while others are more indolent and chronic in nature. The World Health Organization estimates that there are at least 61 types of non-Hodgkin lymphoma, which represents a challenge for the development and delivery of treatments.<sup>3</sup> However, due to the diversity of the disease, in this era of oral therapies, lymphoma can serve as a model for the opportunities and challenges for other cancer types. As such, many of the issues and recommendations identified for lymphoma and CLL have applicability and relevance for the broader cancer community. Therefore, through the dissemination of this White Paper, The Lymphoma Research Foundation seeks to share the findings and recommendations from the Workshop so the insights gleaned can be leveraged to the benefit of lymphoma, CLL, and other types of cancer.

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3 Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, Harris NL, Le Beau MM, Hellström-Lindberg E, Tefferi A, Bloomfield CD (Jul 30, 2009). "The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes." *Blood* 114 (5): 937–51. doi:10.1182/blood-2009-03-209262. PMID 19357394.

## Workshop Background and Agenda

Cancer care has entered a new era in which targeted oral anti-lymphoma agents are quickly changing treatment paradigms. Patients and providers report numerous advantages of oral therapies, including improved quality of life, greater convenience allowing patients to remain at work and receive treatment close to home, and reduced costs for the health care system. Recent survey data has uncovered that up to a quarter – and in some cases even half – of lymphoma or CLL patients are being treated with an oral therapy. While there are many benefits of oral therapy, clinicians note that the shift to continuous therapy also brings with it a variety of challenges and the need to focus on issues such as treatment adherence, cost, value, patient education, measurement of outcomes, monitoring toxicities, and development of new therapeutic endpoints.

Recognizing these important developments, The Lymphoma Research Foundation brought together a diverse set of stakeholders – scientists, clinicians, patient advocates, pharmaceutical industry representatives, federal lawmakers, and federal regulators – for a deep exploration of the current challenges and opportunities in the development, optimization, treatment, adherence, and access to oral therapies for patients with lymphoma and CLL. To ensure a comprehensive examination of the issues relating to the evolving and dynamic development of new oral therapies for lymphoma and CLL, the Workshop program included four main components, focusing on key stakeholder perspectives: Academic; Pharmaceutical and Biotechnology Industry; Patient; and Regulatory and Economic. Specifically, the panel discussions were:<sup>4</sup>

- Use and Study of Oral Therapies in Lymphoma and CLL: Advancing Demographics and Research to Improve Lives <sup>5</sup>
- Emerging Scientific Developments: The Pharmaceutical Industry <sup>6</sup> and Regulatory Landscape
- The Patient Perspective <sup>7</sup>
- The Economics of Oral Therapies: Cost and Care <sup>8</sup>

This White Paper summarizes the presentations and discussions regarding current opportunities and challenges of oral therapies and presents the research agenda, clinical efforts, policy changes, and patient initiatives that scientists, clinicians, and patients believe will help ensure oral therapies are employed optimally. The national research and policy agenda stemming from the Workshop has the promise to deliver better patient outcomes and improve the patient experience for individuals with lymphoma and CLL, as well as other cancers.

<sup>4</sup> To view the full Workshop agenda, including speaker biographies, please see the Appendix.

<sup>5</sup> Scientists on The Lymphoma Research Foundation workshop steering committee discussed opportunities and challenges as they relate to the study and use of oral therapies and identified priority areas for advancing relevant clinical research.

<sup>6</sup> Representatives from industry with oral agents on the market or in the pipeline discussed the current state of the science, the patient experience, regulatory landscape, and areas for collaborative research.

<sup>7</sup> Patient advocates discussed their perspective as it relates to treatment selection, adherence, financial implications, and care planning.

<sup>8</sup> A research scientist who studies the application of decision analysis and cost-effectiveness analysis to issues in breast cancer treatment examined the ways in which financial considerations impact patient access and quality of care.



as patients live with their disease, over time, the goals of treatment for each individual patient may change requiring ongoing discussions regarding the trade-offs between efficacy and tolerability of toxicity. Taken together, the challenges associated with these indolent cancers center on their long-term trajectories and the associated benefits weighed against prolonged toxicity management and lengthened financial implications.

While the heterogeneity of lymphoma brings both challenges and opportunities for research and treatment, particularly within the realm of oral treatment, clinicians and scientists note that it can serve as a useful model and case study for other malignancies, particularly for cancer types for which oral therapies may become available in the future.

**Opportunities and advantages in oral therapies abound but there are numerous reported challenges regarding adherence, monitoring, toxicity management, patient education, and cost.**

There is consensus among scientists, clinicians, and patients that there is an increasing need to better understand and address the challenges associated with oral therapies as well as a growing importance in assessing the value and benefits of these agents.

Patients underscore the need for a wide range of treatment choices, coupled with meaningful information about trade-offs between the conveniences offered by taking an oral therapy versus toxicity and side effect management, so they can make informed decisions about their care. Oral therapies allow patients to move away from receiving frequent treatment in the physician office, infusion center, or other clinical setting to self-dosing at home, shifting much of the responsibility to the patient and away from the clinician. When patients receive infused chemotherapy, they frequently interface with the cancer care team, sharing critical information about side effects, psychosocial status, and other insights and experiences that inform treatment decisions and outcomes. With oral therapies, the patient-provider relationship is vastly different – typically involving only intermittent visits and communication.

In many clinical settings, it may be appropriate to revise the current care infrastructure to address the challenges noted by infusion nurses and physician teams regarding long absences from the patient – not knowing how they are doing or if they are taking the oral therapy as directed. Patients also note that they often miss the comfort and security of being seen in person by their cancer care team regularly (e.g., once or more during each cycle of therapy) and often do not know exactly how to manage side effects or unanticipated events. Some patients report

that they often tolerate certain side effects and toxicities as a necessary trade-off of having the greater convenience of an oral therapy, and do not always share the side effect information with their cancer care team for fear of being taken off of the oral therapy. Scientists and clinicians are interested in examining ways to facilitate and ensure patient adherence to oral therapies while capturing the toxicities and side effects that their patients are experiencing, but not necessarily reporting.

Within the context of oral anti-cancer therapy, scientists, clinicians, and patients all highlight the need for the provision of more supportive care, additional patient education, and patient-centered tools to facilitate treatment adherence, and more creative approaches to securing patient reported outcomes over the course of treatment. Specifically, scientists and clinicians urge greater attention to – and improvements in – the management, monitoring, measurement, and reporting of adverse events, and quality of life. Clinicians note that current data collection underestimates the burden of toxicities of oral therapies and therefore recommend greater investment in the study of side effects. Clinicians articulate the specific need to collect and analyze patient information – in real time – to assess the impact of therapy and determine if a change in treatment or different management of toxicities needs to occur.

While acknowledging the numerous advantages of oral therapy for many lymphoma and CLL patients, scientists and clinicians also express serious concern that the costs of oral therapies can be prohibitive for patients, particularly given the longitudinal nature of some treatment regimens. The combination of an expensive therapy needed for a long period of time can place some options out of patients' reach. Of particular concern is that many Americans face a differential in their insurance coverage between oral anti-cancer therapies and intravenous (IV) treatment. Oral therapies are covered under a pharmacy benefit wherein IV treatment is covered under the medical benefit. This disparity in reimbursement policy often brings with it widely different copayments, coinsurance, and out-of-pocket expenses – making oral therapies too expensive to access for some patients.

Studies have found high out-of-pocket expenses can cause patients to take less than their prescribed dosage, only partially filling prescriptions, and avoiding filling a prescription entirely.<sup>9</sup> Such actions can undermine the efficacy of treatment and, in turn, cause adverse outcomes for the patient. As such, The Lymphoma

<sup>9</sup> Streeter, S. B., Schwartzberg, L., Husain, N. and Johnsrud, M. Patient and Plan Characteristics Affecting Abandonment of Oral Oncolytic Prescriptions. *Journal of Oncology Practice*, 7 (3S), pp. 46s-51s.

Research Foundation and many of the organizations and stakeholders represented at the Workshop have endorsed the Cancer Drug Coverage Parity Act of 2015 (H.R. 2739), introduced by U.S. Representatives Brian Higgins (D-NY-26) and Leonard Lance (R-NJ-7). The legislation, if enacted, would ensure access to oral anti-cancer therapies for patients with commercial insurance by creating parity in coverage for out-of-pocket expenses for oral treatments and infused or IV therapy.<sup>10</sup>

In addition to making oral therapies more affordable and accessible, scientists and clinicians urge that the economic and overall value of oral therapies be assessed.<sup>11</sup> As some oral drugs are taken indefinitely, clinicians urge that studies of the cumulative cost in terms of toxicity, efficacy, and financial burden be undertaken. Further, since the impact of the cost of oral therapies has a direct effect on treatment adherence, scientists recommend specific efforts be initiated to examine the impact of affordability on side effect management and other quality of life (e.g., anxiety) concerns. Clinicians and patient advocacy groups recommend that the patient perspectives on the trade-offs between toxicities and efficacy – as well as cost and value – be factored into the assessments of oral therapies, so that any such evaluations reflect patient treatment priorities and preferences.

Scientists, clinicians, and patients agree that oral therapies bring many advantages but that more must be done to ensure access to the range of available options. The medical and patient advocacy communities needs to promote education on toxicity and side effect management, and identify additional treatment and care options that offer extended survival, reduced side effects, and improved quality of life. Mechanisms to improve quality of life, such as providing psychosocial support for anxiety and stress, may prove to be more appropriate for a particular patient circumstance. Clinicians express deep interest in prioritizing efforts that improve the sense of well-being, particularly for patients with indolent lymphomas.

**Research plays an essential role in ensuring the cancer care team and patients have the information and**

**treatment choices they need to maximize outcomes and ensure quality of life.**

Given the manner in which oral therapies are utilized and monitored, there is a need for new types of clinical trials and other research to assess the benefits and challenges associated with oral anti-cancer treatments. Many clinicians emphasize the importance of evaluating response to therapy with a physician toxicity list and a CT scan response.

Scientists and clinicians recommend a robust research agenda, including: the study of sequencing of treatment; assessment of the dosing, timing, periodicity, and/or discontinuation of therapy; examination of the trade-offs between efficacy and toxicity; evaluation of patient compliance and factors impacting adherence; measurement of treatment durability, safety, morbidity, convenience, and cost; collection of longitudinal data regarding toxicities and patient-reported outcomes; and the identification and evaluation of new endpoints for treatment efficacy.

Traditional clinical trial endpoints within lymphoma and CLL, such as overall survival (OS) and progression free survival (PFS), as well as other measurements, such as minimal residual disease (MRD), pose challenges when attempting to assess efficacy, durability, and value of many new agents. Due to the heterogeneity of lymphomas, scientists and clinicians strongly recommend the study and validation of additional or surrogate endpoints and the development of new ways of measuring effectiveness and toxicity. For example, if a goal of therapy for patients with indolent lymphomas is to feel better and maintain activities of daily living, a therapy that provides measureable symptom relief could be considered an efficacious treatment even if the therapy does not extend overall or progression-free survival. Consideration of surrogate endpoints such as 30-month complete response (CR30),<sup>12</sup> may capture the effect of treatment, but many in the research community believe we need to include composite endpoints that consider toxicity and quality of life, in addition to response rates in incurable, indolent, generally asymptomatic diseases like follicular lymphoma.

**Given the longevity of patients with CLL and indolent lymphomas, safety and tolerability over a longer**

10 The evening prior to the workshop, The Lymphoma Research Foundation invited participants to a dinner at which Representatives Higgins and Lance to speak about the value of oral therapies and the importance of ensuring that as new breakthroughs in treatment are achieved, patients have affordable access to those therapies. They asserted their bipartisan commitment to research funding and securing parity in insurance coverage for oral chemotherapy and urged participants to help them build support in Congress for their legislation.

11 Young RC. Value-based cancer care. *N Engl J Med* 2015; 373:2593-5; Saltz LB. The value of considering cost, and the cost of not considering value. *J Clin Oncol* 2015; online Dec. 28.

12 The Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) group conducted a meta-analysis to establish a novel surrogate efficacy endpoint for progression free survival in first-line follicular lymphoma to be used for regulatory decision making and reduce the duration of clinical trials to expedite patient access to effective new therapies. Patient-level data was obtained from studies that met pre-specified selection criteria, the goal being to perform a meta-analysis designed to identify and establish a surrogate endpoint.

timeframe have become essential in assessing efficacy and value. There is a growing need to better characterize the multiple and chronic toxicities, study and better understand compliance, and examine chronic versus intermittent therapy. For example, clinicians cite the side effects associated with oral therapies for lymphoma and CLL (e.g., diarrhea, rash, bleeding, bruising, fatigue, joint pain) and note a general lack of understanding of the burden of side effects on patients. Due to the nature of most trials and the less frequent contact with patients on chronic oral therapies, the collection and measurement of side effects and toxicities – particularly duration and frequency – currently are incomplete.<sup>13</sup>

Patients express a desire for more complete information and evidence-based protocols as they determine the best treatment path and weigh various trade-offs. Therefore, scientists recommend that toxicities and side effects of oral agents be measured and studied more thoroughly in the context of clinical trials as well as outside the research environment. More robust information is needed about the impact of treatment dosing, frequency, sequencing, and toxicities on patient outcomes and overall sense of comfort.

Scientists and clinicians acknowledge the important role of patients in contributing to the understanding and management of toxicities and informing the development and refinement of outcomes measures (e.g., endpoints, quality measures). Patients on oral therapies have an integral role to play in the design and use of tools to collect and assess information about treatment efficacy and side effects and the impact of toxicities on their well-being. Studies and tools to assess side effects and toxicities inherently must be patient centered since much of the data will be self reported.

Clinicians and scientists also highlight the importance of economic and health systems research and studies to determine value (defined in various ways: economic, clinical, patient priorities, quality of life); cost-effectiveness; medical costs; and other factors to consider in clinical decision-making. As noted earlier, the costs of oral agents often are out of reach for many patients and the overall cost burden of lymphoma and CLL treatment will continue to grow, adversely impacting individuals, families, the health care system, and the government<sup>14</sup>. Clinicians, scientists, and patients all

express support for efforts to assess overall value of oral therapies compared to overall costs. Evaluations should take into consideration the cumulative value and efficacy compared to cumulative toxicity, impact on quality of life, and financial burden for patients with lymphoma and CLL.

13 Due to the nature of most trials and the infrequent contact with patients on oral therapies, researchers and clinicians report that the collection and measurement of side effects and toxicities – particularly duration and frequency – currently are incomplete and in need of significant improvement.

14 Gandhi S, et al. Oral anticancer medication adherence, toxicity reporting, and counseling: A study comparing health care providers

and patients.  
*J Oncol Practice* 2015; 11: 498-504;  
Yabroff KR, et al. Financial hardship associated with cancer in the United States from a population-based sample of adult cancer survivors.  
*J Clin Oncol* 2015; online Dec. 7.

## Workshop Findings and Recommendations

To address these core issues, workshop speakers and participants recommended a number of areas needing attention and action by the private sector, the government, and the patient advocacy community. It is important to note that many of the recommendations have relevance and applicability for the broader cancer community.

### Research Efforts

Additional research is needed to continue to achieve advancements in treatment and care for individuals with lymphoma and CLL.

### Clinical Trials

- Collect acute and longitudinal side effects and toxicity information from clinical trial data. Monitor patients for treatment adherence, side effects, long-term toxicities, and outcomes after a trial has concluded; include the collection of patient-reported outcomes.
- Undertake clinical trials of therapeutic sequencing; the combination of targeted agents; the duration and periodicity of treatment; endpoints for discontinuation of therapy and second responses after treatment interruption. Such studies should assess efficacy as well as safety, treatment-related morbidity, cost, and value.
- Identify surrogate or alternative endpoints, for clinical trials, reflecting therapeutic goals and the heterogeneity of blood cancers to allow the development of therapies that are safe and efficacious, using a broader definition for efficacy that incorporates measures of quality of life and value.
- Increase the number of Phase III clinical trials, create shorter trial periods, develop adaptable clinical trials to promote participation, improve the FDA review and approval process and timeline, and enhance post-FDA approval data collection and analysis.
- Improve control comparators that are clinically meaningful to gauge the risk and benefit of therapies

### Additional Areas of Study

- Undertake comparative effectiveness studies to assess value and effectiveness of therapy.
- Conduct health services and health care utilization research to assess value, including total associated costs, beyond therapy alone. Such studies can be independent or piggy-back on clinical trials.
- Create and maintain registries and other methods to study the natural history of disease. Collect patient experience data to capture real-world longitudinal information about patients on oral therapies, the sequencing and timing of therapies, treatment endpoints and adherence, and the side effects, long-term toxicities, and outcomes.
- Explore lessons learned from other chronic conditions (e.g., HIV/AIDS, chronic obstructive pulmonary disease (COPD), diabetes, heart disease) with respect to adherence, trade-offs of toxicity and efficacy, and value.
- Factor in the role of oncology nurses to facilitate patient education on oral therapies, and navigating access to the oral drug; consider the amount of time it may take a patient to secure access to the oral agent (due to the time, health insurance, utilization of patient assistance programs, etc.) and the impact of delay on the selection of therapy.

## Clinical Efforts

Clinicians, scientists, and patients note the important role of the cancer care team in conducting research; communicating with patients about treatment, side effects, and clinical trials; and supporting patients through direct clinical care and ongoing supportive efforts, including oral treatment education and toxicity management. Specifically, the cancer care team should:

- Support patients in making more informed choices. Specifically, the cancer care team should communicate clearly with patients regarding: the particular goals of therapy and expectations (e.g., cure, palliation, survival, symptom management); care planning; sequencing and timing of therapies; and toxicities and side effects associated with various treatment options.
- Educate patients about the importance and value of participating in clinical trials, surveys, and other efforts to collect patient experience data to inform research and clinical efforts. Patients should be provided an easy-to-use tool (e.g., The Lymphoma Research Foundation Focus on Lymphoma mobile app) – and otherwise be engaged in efforts – to capture acute and long-term adherence, toxicity, side effect, and other information.
- Provide specific and ongoing patient education regarding the benefits and challenges of oral therapy. The cancer care team should seek to better understand patient barriers to therapy, identify any access issues, and seek to ameliorate their adverse impact on patient health and well-being.

## Policy Efforts

Scientists, clinicians, and patients agree that there are numerous areas in which the federal government can support the advancement and accessibility of oral therapies for lymphoma and CLL. Specifically, the U.S. Congress should:

- Urge the National Cancer Institute (NCI) to fund research to study the toxicity and effects associated with long term treatment, including oral therapy.
- Encourage the Patient Centered Outcomes Research Institute (PCORI) to fund more patient-centered outcome, quality of life, and health services research studies associated with the use of oral therapies, including long term treatment impact.
- Ensure affordable access – for Medicare and Medicaid beneficiaries and patients with commercial insurance – to all FDA-approved oral and infused anti-cancer therapies. As part of this effort, Congress should enact oral chemotherapy parity legislation.
- Encourage the FDA to collaborate with industry and researchers on acceptable trial design and endpoints, looking beyond those traditionally used in lymphoma and CLL to reflect the nature of indolent blood cancers. For example, a therapy that offers a better quality of life but may be less efficacious could be an acceptable endpoint for approval. The FDA should fully engage stakeholders to advance new trial designs and endpoints that reflect the opportunities and challenges in oral therapies for lymphoma and CLL.

## Patient and Advocacy Efforts

Scientists, clinicians, and patients commend The Lymphoma Research Foundation for its patient support services, provider education programs, and leadership role in advocating policies that seek to increase access to oral and novel therapies for patients with lymphoma and CLL. Specifically, the Foundation should maintain current efforts and, in addition, should:

- Continue to educate patients about the importance of participating in clinical trials and otherwise sharing their treatment experiences to inform research efforts and clinical practice. As part of this effort, The Lymphoma Research Foundation should leverage its Focus on Lymphoma app and support patients in: capturing, reporting, and facilitating adherence; tracking acute and long-term toxicities; reporting side effect information; and providing other patient-reported outcomes.
- Develop meaningful medical education regarding oral therapies and the challenges and opportunities for patients.

## Summary

The Lymphoma Research Foundation hosted the *Oral Therapies in Lymphoma Workshop* to identify opportunities and actions to address challenges related to the development of – and access and adherence to – oral anti-cancer therapies for lymphoma and CLL, a diverse set of orphan diseases. The Workshop’s panelists presented issues at the intersection of science and policy, which have been described throughout this document. Many of the issues and recommendations raised over the course of the Workshop have relevance not just for oral treatments in lymphoma and CLL but to other oncologic malignancies.

The Lymphoma Research Foundation hopes this White Paper will inform decision-making within the public, private, and non-profit sectors and help guide prioritization of allocation of research resources, contribute to the design of research, and facilitate advancements in treatment, monitoring, and outcomes for patients. In the months ahead, the Foundation will work with stakeholders in the cancer community to pursue the recommendations and undertake action items identified during the workshop.

## Acknowledgements

The workshop co-chairs, Dr. Jonathan Friedberg and Dr. Michael Williams, the Workshop steering committee – Neil E. Kay, M.D., John P. Leonard, M.D., and Sonali M. Smith, M.D., and The Lymphoma Research Foundation wish to extend their gratitude to the presenters at the Oral Therapies in Lymphoma workshop. The Lymphoma Research Foundation also appreciates the time and diligence the workshop co-chairs and steering committee spent in reviewing and contributing to this document. In addition, we would like to thank Congressman Brian Higgins, Congressman Leonard Lance and their respective staffs for leadership on the oral therapies issue, and for their participation in the Workshop. Lastly, the Foundation would like to thank the workshop’s pharmaceutical partners for their support and participation on the discussion panels: Pharmacyclics, Celgene, and Gilead Sciences.

## Appendix

1. Program Agenda
2. Steering Committee Members
3. Speaker Biographies
4. Glossary of Terms

## Agenda

THURSDAY, SEPTEMBER 10, 2015

- 6:00 PM** Registration
- 6:30 PM** Welcome Dinner
- 7:30 PM** Presentation: Access to Innovation  
Currently, many patients pay significantly more out-of-pocket for oral cancer treatments than they do for intravenous treatments. During this session, members of the U.S. Congress will speak to the importance of patient access to new, targeted anti-cancer therapies and their motivation for writing and sponsoring federal legislation that would provide for equal access to these treatments, the origins of many of which were federally-funded research projects.
- Welcome:  
Michael E. Williams, M.D., ScM, *University of Virginia Health System and Cancer Center*
- Speakers:**  
The Honorable Brian Higgins, *U.S. House of Representatives (NY-26)*  
The Honorable Leonard Lance, *U.S. House of Representatives (NJ-7)*

FRIDAY, SEPTEMBER 11, 2015

- 7:30 AM** Breakfast
- 8:00 AM** Welcome and Workshop Overview  
Jonathan W. Friedberg, M.D., M.M.Sc, *University of Rochester Medical Center*
- 8:15 AM** The Use and Study of Oral Therapies in Lymphoma and CLL: Advancing Demographics and Research to Improve Lives
- The development and expanded use of novel oral therapies profoundly impacts the future of lymphoma and CLL care. Panelists and participants are invited to discuss opportunities and challenges as they relate to the study and use of oral therapies, and to identify priority areas for advancing relevant clinical research.
- Speakers:**  
Lymphoma Overview: Clinical Applications and Value for Oral Therapeutics  
Sonali Smith, M.D., *The University of Chicago*  
Treatment Decision Points  
Neil E. Kay, M.D., *Mayo Clinic College of Medicine*  
Monitoring and Reporting  
John P. Leonard, M.D., *Weill Cornell Medical Center*
- Moderator:  
Michael E. Williams, M.D., ScM., *University of Virginia Health System and Cancer Center*
- 9:15 AM** Panel discussion and Audience Questions
- 9:45 AM** Break

**10:00 AM** Emerging Scientific Developments: The Pharmaceutical Industry and Regulatory Landscape  
The rising number of oral therapies for lymphoma and CLL, both currently marketed and in the development pipeline, will significantly impact most aspects of lymphoma care. This panel will discuss the current state of the science, the patient experience, regulatory landscape, and areas for collaborative research.

Speakers:

Joel Beetsch, PhD, *Vice President, Patient Advocacy, Celgene*

Danelle F. James, M.D., M.A.S., *Head of Oncology, Pharmacyclics*

R. Angelo de Claro, M.D., *Medical Officer Team Leader, Division of Hematology Products, Office of Hematology and Oncology Products/ Center for Drug Evaluation and Research/ U.S. Food and Drug Administration*

Moderator:

Jonathan W. Friedberg, M.D., M.M.Sc, *University of Rochester Medical Center*

**11:00 AM** Panel Discussion and Audience Questions

**12:00 PM** Lunch

Presentation: The Patient Perspective

Over the course of the last decade, increasing attention from patients has focused on the efficacy, value, cost and convenience of oral cancer therapy; over this same time period, the number of available agents for lymphoma and CLL patients has grown. As a result, oral cancer therapy is emerging as an important option for patients who can manage the prescribed regimens and recognize possible complications. Certain patients may select an oral treatment because of the appeal of prolonged remission; the perception that it is more convenient to administer; elimination of frequent office visits; or a greater sense of control over their own cancer care. This panel will explore the patient perspective as it relates to treatment selection, adherence, financial implications and care planning.

Speakers:

Geoffrey Grubbs, *The Lymphoma Research Foundation Ambassador, Patient Advocate*

Mitchell Orfuss, *Patient Advocate*

Moderator:

Meghan Gutierrez, *The Lymphoma Research Foundation*

**1:00 PM** The Economics of Oral Therapies: Cost and Care

As the number of oral anti-cancer medications rise, so too does concern about patients' ability to access and pay for these treatments, as recent trends in insurance coverage place a significant financial burden on many people. All of this at a time when the nation works to control total health spending. This session will examine ways in which financial considerations impact patient access and the quality of care.

Speaker:

Elena Elkin, PhD, *Memorial Sloan Kettering Cancer Center*

Moderator:

Michael E. Williams, M.D., ScM., *University of Virginia Health System and Cancer Center*

**1:30 PM** Discussion and Audience Questions

**1:45 PM** Workshop Summary and Next Steps

Moderators:

Michael E. Williams, M.D., ScM., *University of Virginia Health System and Cancer Center*

Jonathan W. Friedberg, M.D., M.M.Sc, *University of Rochester Medical Center*

## Workshop Steering Committee Members

The laboratory research of **Neil E. Kay, M.D.**, is focused on B-chronic lymphocytic leukemia (CLL). This most common and still incurable leukemia is not fully understood in terms of both its clinical and biologic heterogeneity. However, because it is both a frequently diagnosed leukemia and provides ready access to leukemic cells, it proves to be an ideal tumor model for a variety of in vitro studies.

To support the laboratory studies described below, Dr. Kay and his colleagues have established an extensive CLL tissue bank and clinical database that is a rich, nationally recognized resource for CLL studies.

Dr. Kay's work involves close collaboration with several other talented scientists at Mayo Clinic, including Diane F. Jelinek, Ph.D., in the Department of Immunology; Curtis A. Hanson, M.D., and Daniel L. Van Dyke, Ph.D., in the Department of Laboratory Medicine and Pathology; James R. Cerhan, M.D., Ph.D., in the Division of Epidemiology; and Susan L. Slager, Ph.D., in the Division of Biomedical Statistics and Informatics. This collaboration has provided for unique studies in CLL that now include extramurally funded studies in CLL B-cell signaling, detailed epidemiological studies of CLL and genome-wide analysis of familial CLL patients (CLL families with two or more CLL patients). Dr. Kay is also very involved in the design and implementation of CLL clinical trials for previously untreated and treated CLL patients that incorporate the latest novel drugs alone or in combinations. These trials are conducted within the national cooperative group system of the United States.

**John P Leonard, M.D.**, is the Richard T Silver Distinguished Professor of Hematology and Medical Oncology and Associate Dean for Clinical Research at the Weill Cornell Medical College. He is Vice Chairman for Clinical Research of the Department of Medicine and Associate Director of the Cancer Center at Weill Cornell Medical College and New York Presbyterian Hospital, where he also serves as Attending Physician, Chief of the Lymphoma Service and Director of the Joint Clinical Trials Office in New York City. He received his medical degree from the University of Virginia School of Medicine in Charlottesville, and completed his residency in medicine at New York Hospital - Cornell Medical Center and Memorial Sloan-Kettering Cancer Center.

Dr. Leonard completed a fellowship in hematology and oncology at Cornell, and served as chief medical resident at New York Hospital - Cornell Medical Center. His primary research interest is in the development of novel therapeutic strategies for the treatment of lymphoma and related hematologic malignancies. Much of his work has involved the development of novel therapies for lymphoma, including monoclonal antibodies, other immune-based treatments, targeted agents, and other innovative approaches.

Dr. Leonard's research has been published in numerous medical journals, and he has served as a member of the editorial boards of *Blood* and *Journal of Clinical Oncology*, leading international journals in these fields. He is Chair of the Lymphoma Committee of the Alliance for Clinical Trials in Oncology, a multicenter cooperative group and key component of the National Cancer Institute's National Clinical Trials Network. Dr Leonard is an elected member of the American Board of Internal Medicine and American Society of Clinical Investigation.

**Sonali M. Smith, M.D.** is an expert in the care and treatment of adults with all types of Hodgkin and non-Hodgkin lymphoma. She has a special interest in new agents for lymphoma, as well as stem cell transplantation and its role in improving the survival of patients with relapsed lymphomas.

An active researcher, Dr. Smith is involved in the development of promising agents for patients with non-Hodgkin and Hodgkin lymphoma. She is principal investigator on a number of innovative clinical trials. Many of the trials incorporate the collection of tumor and blood samples to study the effects of treatment on cancer cells through collaborative laboratories.

Dr. Smith frequently lectures to both physicians and patient groups on these topics. She serves on several national committees charged with improving treatment options for patients with lymphoma, providing physician education, and providing reliable information for patients through established websites. Dr. Smith also frequently performs peer reviews of research being considered for publication in major medical journals. Additionally, she has won several teaching awards at the University of Chicago.

## Speaker Biographies

**Dr. Joel Beetsch** currently holds the position of Vice President of Patient Advocacy within the Celgene Corporate Affairs Department. In this position, Dr. Beetsch leads the global development and execution of a coordinated patient-focused Advocacy strategy working with multiple patient, provider, payer, and policy organizations to foster safe and effective solutions to healthcare challenges. These efforts drive the assurance that patient access to healthcare solutions and medical innovation and are valued and advanced.

During his 15 year tenure in the biopharmaceutical industry, Dr. Beetsch has held several Medical and Corporate Affairs positions. Joel has professional interests in patient-focused care coordination, health policy, and the use of health information technology.

Joel earned his Doctorate in Neurobiology/Biochemistry from the Boonshoft School of Medicine at Wright State University. Following his doctoral work, Dr. Beetsch was further trained in cellular physiology at the Washington University School of Medicine in St. Louis.

**Dr. R. Angelo de Claro** is a Clinical Team Leader with the Division of Hematology Products, Office of Hematology Oncology Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration. He received his M.D. degree (magna cum laude) in 1998 from the University of the Philippines. He completed his Internal Medicine residency at Baylor College of Medicine (Houston, TX), and his Hematology-Oncology fellowship at University of Washington (Seattle, WA). He joined FDA as a medical officer in 2010, and became a clinical team leader in 2012. Currently, he provides leadership to a team of clinical reviewers who review drug applications for benign and malignant hematology indications.

**Dr. Elena Elkin** is an Associate Attending Outcomes Research Scientist in the Center for Health Policy and Outcomes at Memorial Sloan Kettering Cancer Center. Her research addresses the determinants of cancer screening, treatment and outcomes using population-based observational data analysis, decision analysis and survey research methods.

She has a special interest in the economic impact of cancer treatment on patients, their families and the health care system, and understanding and improving clinical decision-making processes from both patient and provider perspectives. She has studied the cost and cost-effectiveness of treatment strategies in breast, prostate, pancreatic and

other cancers, and she is currently leading economic analyses alongside clinical trials of behavioral and preventive interventions in childhood cancer survivors and low-income minority patients. She also studies treatment patterns, complications and costs in non-Hodgkin lymphoma, urologic and other cancers in the population-based SEER-Medicare dataset.

She has a PhD in Health Policy from Harvard University and a Masters in Public Administration from NYU.

**Geoffrey Grubbs** was diagnosed in 2009 with chronic lymphocytic leukemia/small lymphocytic lymphoma. He has had general immune system failure, but is currently following a watch and wait approach. Geoff feels good and continues to be active in with local events of The Lymphoma Research Foundation and advocacy activities. He also participates each year in the Lymphoma Research Ride. He lives in Washington, DC with his wife.

Geoff also serves as The Lymphoma Research Foundation Ambassador. The Ambassador Program is the first-of-its-kind program to formally media train lymphoma patients, survivors and caregivers to serve as spokespeople for the disease and for the organization. The Lymphoma Research Foundation Ambassadors represent a variety of lymphoma subtypes and experiences. Through the annual training program, The Lymphoma Research Foundation Ambassadors learn to effectively share their stories for a variety of audiences and media outlets in order to garner the most impact.

**Meghan Gutierrez** is Chief Executive Officer (CEO) of The Lymphoma Research Foundation, the nation's largest non-profit organization devoted exclusively to funding lymphoma research and providing patients and health care professionals with critical information on the disease. Gutierrez has focused her entire career in the government and philanthropic sectors, beginning as a Congressional staff member for one of the U.S. House of Representatives' foremost leaders on health care policy, then shifting to the non-profit arena, working on an array of health-related issues, ranging from mental health parity and rare disease awareness to medical technology and the treatment of chronic disease.

**Congressman Brian Higgins** is a member of the United States House of Representatives serving New York's 26th congressional district, which includes portions of Erie and Niagara Counties. Brian is a member of the Congressional Cancer Caucus, Co-Chair of the newly created National Institutes of Health Caucus and a consistent voice for cancer patients in Western New York and on Capitol Hill.

This year the Congressman introduced the Accelerating Biomedical Research Act, bipartisan legislation that would add over \$57 billion in new funding over the next six years to the National Institutes of Health in addition to the \$29.9 billion in annual NIH baseline funding. Brian has also been a leader on legislation, H.R. 2739, the Cancer Drug Coverage Parity Act, which would ensure insurance parity for oral chemotherapy drugs, and previously testified before the House Budget Committee calling for the doubling of the nation's commitment to cancer research.

In the 114th Congress, Brian continues to serve on the House Committee on Homeland Security and the House Committee on Foreign Affairs. Congressman Higgins was an instructor in the History and Economics departments at Buffalo State College, where he had previously earned his undergraduate degree in Political Science. Brian also earned an advanced degree in Public Policy and Administration from Harvard University's John F. Kennedy School of Government.

**Dr. Danelle James** is Head of Oncology at Pharmacyclics where she leads clinical development efforts for CLL/SLL, Graft vs Host Disease, and Solid Tumors. Prior to joining Pharmacyclics in 2011, Dr. James was a faculty member in the Department of Medicine, Division of Hematology and Oncology at University of California San Diego. Her research focus at UCSD for ten years, was the study of the Chronic Lymphocytic Leukemia (CLL) and the tumor microenvironment and the clinical-translational development of agents that can be used to target these interactions.

As a leading member of the CLL Research Consortium (CRC), she co-coordinated the clinical trials program evaluating the combination of novel agents for the treatment of CLL.

Danelle started her career in industry 18 years ago at Biogen in Cambridge Massachusetts where she conducted research in the Immunology and Inflammation Department. Dr. James completed Internal Medicine residency and Hematology/Oncology fellowship at UCSD, is Board Certified in Internal Medicine and in Hematology. She obtained formal education in clinical research methodologies and a Masters degree in Advanced Studies of Clinical Research from UCSD.

**Congressman Leonard Lance** represents the Seventh Congressional District of New Jersey and serves on the House Energy and Commerce Committee and its Health Subcommittee. He also chairs the bipartisan Rare Disease Caucus and founded the Deadliest Cancers Caucus with colleagues who are dedicated to research and medical innovation. Through these platforms Lance advances a proactive agenda of advancing medical and biopharmaceutical research and development, championing the fight of countless advocates who seek new cures for loved ones, and promoting legislation that will continue to strengthen and accelerate the pace of cures in the 21st century and keep patient care at the forefront of every debate. He has also championed legislation that addresses our Nation's ailing mental health care system, increases information on unmet medical needs and boosts resources for research. He is also active on the Energy

and Commerce Committee's 21st Century Cures Initiative, which is designed to find ways to improve the drug development process from discovery to development to delivery. He has spent much of his congressional career to championing opening the innovative pipeline and to tackling one of the great public health challenges: cancer. To this end has introduced the bipartisan Cancer Drug Parity Act, legislation that would require health insurance plans that cover traditional chemotherapy provide equally favorable coverage for orally-administered anticancer medications.

**Mitchell Orfuss** learned unexpectedly that he has Waldenstrom's macroglobulinemia in 2002. Mitch continues to work full-time, and supports The Lymphoma Research Foundation and the International Waldenstrom's Foundation (IWMF) by volunteering to lead its New York Metro-Area Support Group and by participating on the Foundation's fund-raising committee. The International Waldenstrom's macroglobulinemia Foundation is a patient-founded and patient-led, nonprofit organization that is dedicated to supporting everyone affected by Waldenstrom's Macroglobulinemia while advancing the search for a cure. He lives with his wife of 29 years, has two semi-launched kids in their mid-twenties, and has been a committed daily aerobic exerciser for 50 years.

## Glossary of Terms

**adverse reaction:** A side effect caused by a drug or therapy.

**aggressive lymphomas:** Lymphomas that are fast growing. These types of lymphoma generally need to be treated immediately, but there is a good chance for a long-term cure. These lymphomas are also called intermediate-grade or high-grade lymphomas.

**chemotherapy regimen:** Combinations of anti-cancer drugs given at a certain dose in a specific sequence according to a strict schedule.

**CT or CAT (computerized axial tomography) scan:** This imaging test provides a series of detailed pictures of the inside of a body using an x-ray machine linked to a computer.

**event-free survival (EFS):** The period of time starting from treatment in which no defined events (disease progression or death) occur.

**indolent lymphoma:** Lymphoma that grows slowly and often has few symptoms. Also called low-grade lymphoma.

**minimal residual disease (MRD):** the name given to small numbers of leukaemic cells (cancer cells from the bone marrow) that remain in the patient during treatment, or after treatment when the patient is in remission (no symptoms or signs of disease). It is the major cause of relapse in cancer and leukemia.

**overall survival:** a statistical term referring to the percentage of people in a group who are alive after a defined length of time – usually years.

**progression-free survival (PFS):** The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse.

**refractory disease:** A cancer that is resistant to treatment.

**regimen:** A specific combination of drugs (chemotherapy), their doses and their schedules of administration. A regimen may also include radiotherapy.

**remission:** The absence of disease. Remission does not necessarily mean cure. A patient is considered in remission when the lymphoma has been treated and tumors have diminished by at least 50 percent (partial) or have totally disappeared (complete).

**toxicities:** The unwanted side effects of cancer therapies, such as decrease in blood cells, nausea and vomiting, and hair loss.



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