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Recent Advances and Future Directions in Follicular Lymphoma:

Proceedings of the 2022 International Follicular Lymphoma Scientific Workshop

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Abstract

Follicular lymphoma (FL) is an indolent form of non-Hodgkin lymphoma that remains incurable. Although patients have high response rates to therapy, most of them will develop increasingly resistant disease and the indolent lymphoma can trans-forms into an aggressive lymphoma, which is associated with poor outcomes. Recent clinical trials have provided insight into the efficacy and safety of various therapeutic strategies, yet aligning treatment with the underlying tumor biology and treatment sequencing remain key clinical challenges. Several novel agents are being developed, and early clinical data are promising. At the Lymphoma Research Foundation's inaugu-ral 2022 FL Scientific Workshop, experts convened to discuss the current standard of care, highlight unmet patient needs, present data regarding newly approved and emerging agents, and suggest optimal approaches for designing future clinical trials and treatment regimens. This report, which includes a summary of each presentation, aims to review recent research findings in FL research and highlight potential areas for future study.

2022 International Follicular Lymphoma Scientific Workshop Steering Committee

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Introduction

Follicular lymphoma (FL) is an indolent B-cell non-Hodgkin lymphoma (NHL), with the majority of patients harboring the *t(14;18)* chromosomal translocation, resulting in overexpression of the BCL2 protein. Chromatin modifying mutations are a common feature of the disease, and the tumor microenvironment (TME) plays a key role in the underlying biology. Progress in drug development has allowed for the majority (~80%) of patients to achieve an overall survival (OS) of 10 to 15 years or more. However, the natural history of indolent FL disease can include histologic transformation to a higher-grade subtype, including diffuse large B-cell lymphoma (DLBCL), and is typically associated with poor patient outcomes. While most patients will respond to the current standard of care, many of them will relapse and require intermittent treatment throughout their lifetime. Consequently, there are a number of unmet patient needs, including aspects of quality of life (QoL) that require improvement. Understanding the marked heterogeneity of FL remains a challenge at both the biology and clinical levels. Cross-disciplinary collaboration is critical to better understand the disease and devise solutions to address existing gaps in patient care.

The Lymphoma Research Foundation (LRF), the nation's largest non-profit organization exclusively dedicated to lymphoma research and patient advocacy, hosted the inaugural 2022 International Follicular Lymphoma (FL) Scientific Workshop, which was funded through the LRF Jaime Peykoff Follicular Lymphoma Initiative. Through the generosity of the Peykoff Family, five high-impact research grants were awarded to senior investigators and an additional five grants were awarded to early career investigators. At the Workshop, the five senior awardees presented the aims of their grants, along with preliminary data. Attendees, comprised of expert lymphoma researchers and clinicians, discussed the latest research findings, clinical trial results, unmet patient needs, and future priorities related to the biology and treatment of FL. This report of the Workshop proceedings spotlights the most promising lymphoma researchers who have the greatest potential to improve patient care and outcomes. Each presentation was followed by a detailed discussion among speakers, moderators, and attendees who raised key questions, emphasized unmet gaps, and proposed practical solutions to further advance the field. A brief summary of areas of unmet needs, gaps, critical research areas, and treatment controversies are provided at the end of each session.

Proceedings

Introductory Remarks – *Meghan Gutierrez, CEO, Lymphoma Research Foundation, and Sonali Smith, MD, The University of Chicago, Chair, Lymphoma Research Foundation Scientific Advisory Board*

To commence the workshop, Meghan Gutierrez (Lymphoma Research Foundation) welcomed attendees, emphasizing the heart of the Jaime Peykoff Follicular Lymphoma Initiative is to bring together a collaborative effort of scientists, clinicians, patients, and advocates to develop new treatments and a cure for follicular lymphoma (FL). She expressed her gratitude to the Peykoff Family, who has enabled the development of this first-of-its kind effort focused on FL. The multi-year, $10 million initiative is composed of the inaugural 2022 International Follicular Lymphoma Scientific Workshop, and funds research grants awarded to both senior and early career investigators focused on the unique gaps in etiology, biology, treatment, and patient care. Notably, the LRF serves a community composed of nearly 1 million patients and caregivers, with a unique focus on patient education. This program intends to bring the latest research findings, clinical trial information, and sophisticated information about the care of patients with FL to both patients and their caregivers. She concluded by recognizing the dedication and efforts of the LRF Board of Directors, LRF staff, Steering Committee, and Scientific Advisory Board for spearheading and developing the program.

Sonali Smith, MD (The University of Chicago) warmly welcomed attendees and expressed gratitude to the Scientific Advisory Board for their countless efforts in devising this Workshop. She described the overall challenges associated with FL, particularly in terms of the biology, potential for transformation, and numerous unmet needs for patients. She outlined the gaps and themes that emerged from the LRF's FL Discovery Workshop held in June 2020. Lastly, Dr. Smith drew attention to the first ten FL grants made possible through the generosity of the Peykoff Family and LRF donors, including five senior investigators who presented their grant details at this Workshop:

- Stephen Ansell, MD, PhD (Mayo Clinic, Rochester), The Immunological Phenotype of Intratumoral T-cells in Follicular Lymphoma;
- Todd Fehniger, MD, PhD (Washington University St. Louis), NK Cell Biology and Therapy for Follicular Lymphoma;
- Abner Louissaint, Jr, MD, PhD (Massachusetts General Hospital), Interplay of Microenvironment and Epigenetics in a Novel Model of FL;
- David Scott, PhD, MBChB (BC Cancer, Vancouver), Four-Dimensional Characterization of FL to Predict Clinical Trajectory; and
- Hans-Guido Wendel, MD (Memorial Sloan Kettering Cancer Center), Understanding and Therapeutically Targeting Epigenetic Drivers of Oncogenesis and Immune Evasion in FL.

Session I: Prognostic and Risk Factors – *David Scott, MBChB, PhD, BC Cancer, Provincial Health Services Authority (Senior Investigator Grant Awardee)*

To open the session, David Scott, MBChB, PhD presented the aims of his research grant, "Four-Dimensional Characterization of FL to Predict Clinical Trajectory." Prognostic and predictive biomarker development in FL has proven to be extremely challenging, not only because of disease heterogeneity, but also heterogenous treatments and endpoints (i.e., combining progression and transformation), which in turn, impact biomarker performance. Importantly, the proportion of progression vs transformation changes with the efficacy and type of treatment. The goals of this research grant are to identify molecular subgroups within patients with advanced stage FL who required treatment and to leverage this improved understanding of genetic aberrations and the TME to allow for the development of biomarkers for both progression and transformation. This will be accomplished using a population-based cohort treated with modern immunochemotherapy (i.e., BR) to maximize generalizability to the real-world standard of care (SoC) setting. The study cohort consists of 256 patients diagnosed and/or treated from 2013 to 2018 from a previous

study [Freeman, 2019] and are representative of patients treated in real-world settings. From that study, 180 patients had sufficient material to be included in a tissue microarray (TMA). Only 15% of the total study cohort experienced a POD24 event and 11% had clinical transformation, which appeared to be unaffected by the introduction of BR vs the previous SoC of R-CVP. In aim 1, the molecular subtypes will be defined by examining the relationships between the "four-dimensions," which are genetic aberrations, gene expression, malignant cell protein expression, and TME composition and architecture. Whole exome sequencing, ribodepletion RNA-Seq, and imaging mass cytometry will be used to study the relationships between the "four-dimensions." Aim 2 is to use a combination of patient characteristics and the "four-dimensions" to design prognostic and predictive biomarkers for FL progression and transformation. This will be accomplished by testing previously described biomarkers of FL in BR-treated patients of the population-based cohort, including the m7-FLIPI and the 23-gene expression assay. The study will also examine the prognostic power of molecular subgroups defined in Aim 1. The overall goal is to translate these data into tractable assays and test them in cohorts of patients treated with other modern regimens in collaboration with clinical trials and other groups to test the predictive nature of these biomarkers.

Panel discussion
Following the presentation, the floor was opened for comments and questions. The following points were raised by audience members for consideration:

- Most transformations among BR-treated patients occurred within the first 3 years—is this biology, or are we simply missing transformation present at diagnosis that presents after therapy? Can you really explore this question from a single-site pathological sample?
  - o Dr. Scott: We need to think about using circulating tumor DNA (ctDNA) and other technologies that will integrate the geographical heterogeneity of FL.

- What is the reason for the discrepancy between the total number of patients and those included in the TMA cohort?
  - o Dr. Scott: The drop between the ~300 patients clinically identified and those that made it into the study (256 patients) was based on diagnoses made on bone marrow and then on others made on tiny biopsies. The drop between the 256 patients and the 180 patients was because people had used core needle biopsies to make the diagnosis. In the British Columbia (BC), we now see people using 60% to 70% of core needle biopsies for all lymphomas, whereas it used to be 10% to 20%. Despite guideline recommendations, people are increasingly using core needle biopsies to make diagnoses. In FL, it is particularly important to get a good biopsy to examine transformation and get the correct diagnosis.

- Have you thought about trying to devise a method to capture either the mutation(s) using ctDNA or other assays that will eventually provide better a representation of FL heterogeneity?
  - o Dr. Scott: We have thought a lot about this, and it really comes down to the resources you have collected. We already have ctDNA for a small proportion of these patients and will be examining that data. Ideally, at diagnosis, we would sample multiple lymph node sites and compare them across patients, which I think is a project that needs to be conducted.

- To the point of heterogeneity, it looks like the patients were homogeneously treated—did the majority of patients receive BR?
  - o Dr. Scott: Yes, they did, and there was a push for patients to get 6 cycles at that time in BC.

- Is the dataset mainly for discovery or planned external validation?
  - o Dr. Scott: There is another cohort that is R-CVP, and will be looking for clinical trial partners.
    - ■ Dr. Andrew Evens, DO, MSc, FACP (Rutgers Cancer Institute of New Jersey): Robert Kridel, MD, MPH, PhD (Princess Margaret Cancer Centre) could be a possible partner.

- Are you able to look at BCL2 mutations, risk for transformation, and decreased survival?

  o Dr. Scott: Yes, we will use whole exome and in select cases, we will use whole genome analysis including BCL2 translocation-negative FL. We will also perform capture sequencing of break points to further explore the biology and pinpoint cryptic translocations, examining other mechanisms in BCL2 translocation-negative FL.

Lindsay Morton, PhD (National Cancer Institute; Moderator) continued the discussion about prognostic and risk factors by reviewing current outstanding questions and potential opportunities for LRF intervention. FL accounts for about 12% of all mature NHLs, with an increased incidence among older adults, males (slight), and White people. The strongest identified risk factor is a family history of lymphoma, conferring about a two-fold increased risk, and various common genetic variants have been identified for FL.[Cerhan and Slager, 2015] Unfortunately, there is no strong evidence of association for most other lifestyle, medical history, and occupational risk factors.[Linet, 2014] Dr. Morton noted that a different approach needs to be taken, suggesting that risk factors are being missed with current method-ologies. One of the best methods is through consortium approaches, such as the International Lymphoma Epidemiology Consortium (InterLymph). In this consortium, there are more than 20,000 NHL cases and over 4,000 FL cases, with 50% to 60% of them having biospecimens, though most commonly germline DNA rather than tumor specimens. LRF should think about how they view risk factors in terms of targeted etiologic studies of high-risk populations, considering the potential to look at focused exposures. LRF should consider providing support for investigators, particularly in terms of salary and collaborative efforts to investigate risk factors using existing data resources. Genetic and lifestyle risk factor data should be integrated into prognostic studies.[Cerhan, 2007; Chihara, 2021; Geyer, 2010; Strefford, 2021] A major challenge is identifying settings where there are both risk factor and prognosis data. Many questions about integrating risk factor and prognosis data remain, including selection biases, high-quality exposure data, and sufficient clinical trial data.

Next, Andrew Evens, DO, MSc, FACP finished the first session with a robust discussion on clinical prognosis vs prediction. FLIPI-1 uses baseline clinical factors for patients who received non-rituximab therapy and FLIPI-2 was studied among patients who received rituximab-based therapy. Both provided prognostic information. However, neither prognostic scoring contains actional information to predict the effectiveness of different treatments (i.e., a "predictive" clinical or biomarker).

A prognostic factor defines the effects of patient and/or tumor characteristics on outcome regardless of treatment; in contrast, a predictive factor defines the effect of treatment on the tumor, taking into account quantitative (eg, EZH2 mutations) vs qualitative interactions.[Ballman, 2015; Mandrekar and Sargent, 2010; Oldenhuis, 2008] A large chasm exists from prognostic to predictive factors; however, prognostic factors can be used to accurately project individual clinical outcomes to identify predictive factors of treatment effects.[Casulo, 2022]

In a three-arm, phase 2 study of BR with bortezomib induction or lenalidomide continuation in untreated FL (i.e., E2408, aka the BIONIC study), POD24 was observed in 16% of patients, which was strongly associated with inferior OS, and 7% of patients had transformed to DLBCL.[Evens, 2020] An unmet need is knowing what the optimal treat-ment is for a POD24 patient who has received BR and R-CHOP. Another gap is how to get from prognotic to a surrogate marker, with consideration for statistical rigor.[Bachy, 2010; Shi, 2017] A surrogate endpoint has to result in the same inference as if the study had observed the true endpoint, and critically, it must constantly be reassessed with new treatments, mechanisms, and subpopulations.[Mandrekar and Sargent, 2010; Sargent and Mandrekar, 2013]

There is also an issue of multiplicity when trying to convert prognostic to predictive markers. Dichotomizing a variable that has a linear effect leads to loss of statistical power and this should be examined. Greater sophistication and linearity is needed to develop accurate predictive biomarkers.[Bachy, 2021] The way to validate that a prognostic factor is predictive of treatment effect is via a randomized controlled trial (RCT). Multiple baseline factors are prog-nostic of patient outcomes (eg, FLIPI) and there are emerging post-baseline prognostic factors (eg, PET/CT, POD24).

However, there is a need for rigorous statistical and analytic fidelity, perhaps in collaboration with statistical colleagues as prognostic markers are further developed. Finally, the integration of biologic factors (tumor or other) will be critical to enrich prognostication as well as to delineate potential actionable predictive makers.

Panel discussion
Following the presentation, the floor was opened for comments and questions. The following points were raised by audience members for consideration:

- Bruce Cheson, MD, FACP, FAAS (The Center for Cancer and Blood Disorders): Focusing on response-adapted studies should not be the goal; instead, we should be focusing on risk-adapted studies (eg, a patient who has stage III DLBCL vs one with stage II double-hit lymphoma). We need to figure out a way of integrating not only the biology, but also the radiomics and the molecular genetics into our initial assessment. In Hodgkin lymphoma, there are low- and high-risk patients even within limited and advanced stage disease; therefore, there needs to be a better way to classify patients. How do we integrate this data at diagnosis before we subject patients to therapies to which they may not respond?

    o Dr. Morton: How do you see advancing the field the most quickly? Do we do this by bringing candidates forward from small individual studies and bring them together to do one big study, or do we perform a large study up front? Do we already have this data in a lot of places?

        ■ Dr. Cheson: I'm not sure we have the data because we haven't captured it all (e.g., new radiomics), though I do think we should be conducting smaller studies that integrate biological and genetic factors along with risk-adapted strategies. With this consortium here, we can discuss the results of those studies in an integrated way.

- Luis Malpica Castillo, MD (M.D. Anderson Cancer Center): I often advise oncologists working in low-to-middle income countries to not change their practice or get interim PET scans because prognosis and survival will not change. We talk about global collaboration, but how can we actually use this globally? For example, we are not going to be doing sequencing anytime soon in low-income countries and this is not going to be meaningful for practice. How can we actually do this for everyone else that can actually use it in other limited settings?

    o Dr. Evens: We need to consider real-world patients and access issues when devising practical solutions, which will require global collaborations.

    o Dr. Morton: This is similar to community hospitals, and there is a bias towards the major academic centers. However, whole genome sequencing is not happening for every patient, even in academic centers, but there is a lot of promise for doing that type of discovery research in higher-resource settings, so the question becomes, how do you translate it?

- Dr. Scott: I think the task is to continue the very best science, but always be thinking about how we can translate that into practical, accessible tools; if not, it is an ivory tower for the wealthy, which is not the way forward.

- Dai Chihara, MD (M.D. Anderson Cancer Center): Do you think we should have a different endpoint other an OS, such as lymphoma-specific survival? Which patient population with FL would we need to predict a model for, considering there are some patients who do not receive treatment and are fine?

- Dr. Evens: With regard to the dichotomy and simplicity that we currently use, we need more linearity, more discovery, a database, validation cohorts, and so forth. Most people would say that the endpoint should be OS, though another important endpoint is QoL. OS is difficult in a disease with a long natural history, so we are going to need to do more surrogate research, perhaps 30-month complete response (CR) rate.

- Stephen Ansell, MD, PhD (Mayo Clinic, Rochester): Should the focus of predictive vs prognostic markers not be on who is going to do excellently, but rather directed towards higher-risk patients? We already have datasets that are good enough to answer this question.

- Brian Link, MD (University of Iowa): The question then becomes, is telling a patient that they will be fine living with FL good enough for the them?

  o Dr. Ansell: I am not sure, because I would not want to speak for them, though this would be the next set of excellent questions to ask that patient population, if we can identify them. We do have large datasets where we looked at the tail of the elephant, but not the trunk—is it time to look at the trunk?

- Jonathon Friedberg, MD, MSc (University of Rochester): If we could identify the patients who could be cured, that would be more compelling than identifying patients who need rituximab, but will still be burdened with the disease.

- Izidore Lossos, MD (University of Miami Health System): In this disease, it is problematic to know if there is a cure and if we will ever have a cure.

- Joachim Yahalom, MD (Memorial Sloan Kettering Cancer Center): In the context of localized disease only, we have recently identified a group of patients that, with a sublethal dose of radiation, one treatment of 4 Gy compared with 24 Gy will make these patients disease-free for a long time. Is it legitimate to take a patient who is potentially curable and give them one dose of 4 Gy or 2 treatments of 2 Gy and give them a chance of cure with no transformation? We are trying to identifying these patients and have data to compare them with patients that will progress or relapse within 1 year or less. This is a group of patients that we have ignored with past prognostic models, and we should pay more attention to these patients. Additionally, for those patients with advanced stage or relapsed disease, this is an excellent palliative treatment.

  o Dr. Morton: How are you selecting these patients?

    ■ Dr. Yahalom: We have radiomics and gene expression profiles to identify these patients, and we are in the early stages of differentiating which patients have long-term, controlled disease vs those with relapsed disease.

  o Dr. Evens: Can you talk a little more about how you can use radiomics to identify patients?

    ■ Dr. Yahalom: We look at PET and size features, and we have recently published in Blood Advances.[Imber, 2021] We have a prospective randomized study in collaboration with ECOG institutions, and hopefully, will soon have data.

- James Cerhan, MD, PhD (Mayo Clinic, Rochester): What about precursors (e.g., *t(14;18))?* Are there things we can build on from there to help understand etiology? Secondly, when we look at genetic studies, the most provocative signal is from HLA. Do we need strategies to see if we can identify the antigen driving that observation? Could it be an infection, or of autoimmune origin? Thirdly, non-Western, "westernized" populations are seeing increasing incidence rates of FL—is there a way to get insight from this trend?

  o Dr. Morton: Can you measure something that is before the FL, such as the presence of circulating lymphocytes with *t(14:18)* translocations, and what does that mean for disease? Can we profile the tumors and get at their etiology? Is it both a risk factor and predictive or prognostic, depending on the model and study design?

  o Dr. Evens: Industry colleagues are not as interested in risk-factor etiology, so the people who could have an impact in this area would likely be the National Institutes of Health (NIH) or LRF.

  o Dr. Smith: What are some of the existing genetic backgrounds of patients who are prone to developing FL? We could partner with clinical cancer genetics programs that focus on heme malignancies (e.g., the University of

Chicago has datasets of families with multiple heme malignancies). We could use that information for etiology and prognosis. We may be able to identify risk factors for who will have early transformation using deeper sequencing.

- o Dr. Morton: What is the genetic architecture on the germline side for FL? Can we use diseases outside of lymphoma or heme malignancies as a model? What other cancers are there that we cannot find risk factors for or clear high-risk families?

- Dr. Scott: We can examine common precursor cells (CPCs) by doing serial samples, and we have been doing this in DLBCL, particularly in patients who relapse after 2 years. We see that these tumors are very different, with core sets of shared mutations. From that data, we infer there is a CPC that has given rise to two transformations. These patients respond to therapy and autologous stem cell transplant, whereas the patients who relapse within 9 to 12 months are the ones who have disease, have been exposed to chemotherapy, and are resistant. This may be the same story in FL. Is cure about eliminating that CPC population down to a level that the immune system can take care of, or are there mutations that actually suppresses transformation? Maybe we should be thinking about late relapses differently and not thinking that it is the same FL back again, but actually another event that has occurred.

- o Dr. Morton: Regarding the design of such a study, would we need whole genome sequencing and would that be possible?

  - ■ Dr. Scott: We are doing whole genome sequencing and then very deep panel sequencing on a number of mutations.

- o Dr. Morton: It is complicated, but it is important to use other models and figure out how to apply them in FL. Are there settings in which you can take additional samples for research purposes and do more biopsies in a limited set of patients?

  - ■ Dr. Scott: It would require a prospective study design and have a lot of patients to get that picture.

- Gilles Salles, MD, PhD (Memorial Sloan Kettering Cancer Center): Are we missing something at the level of cellular interactions and immune components, or exogenic factors that may help these CPCs to progress disease, and how can we address this? Are we connected to enough lymphocyte biology researchers? Do we have sufficient tools to analyze epidemiology cohort data? Finally, are we not selecting different clones or cell populations with treatment?

- o Dr. Scott: We have observed that the 23-gene predictor is flipped between patients treated with R-CHOP and BR; thus, it is a predictive biomarker and needs to be validated. We could potentially use the 23-gene predictor to guide treatment selection.

- Ari Melnick, MD (Weill Cornell Medicine): One thing that is different about precursor B-cells from lymphomas is that B-cells are incredibly heterogenous. Even within FL or DLBCL, the B-cells are not uniform, making it quite difficult to have a flow marker to identify a CPC. The genetic features are probably a better way to go after the CPCs, but it is still difficult to know since almost everyone has these cells and it would be difficult to predict if any of these could progress to lymphoma. This is perhaps where some of the more innovative cell-free methods could be helpful to go beyond somatic mutations, which could be epigenetic, chromatin-type methods. Until we can isolate these cells out efficiently, those kinds of methods could be the best. Furthermore, we may be able to apply biological aspects of the disease to experimental diagnostic studies, such as following the progression of epigenetic modifiers over time.

- Anne Novack, PhD (Mayo Clinic, Rochester): We looked at tumor genomes via RNA-Seq in germline and identified predictors of early clinical failure, such as EFS24.

    o   A component of that project was to bring together about 15 observational datasets to model FLIPI24. We are seeing a shift in the cumulative incidence of less progression, and transformation rates are staying the same on BR vs R-CHOP. Percentage-wise, it appears like there is more transformation, but at a cumulative incidence, it is not changing. The early transformers do very poorly, but even the progressions are not doing great. We have to think about both progression and transformation, which gets back to the initial question of, what have we sampled at the initial diagnosis? Is this FL or was there DLBCL and we missed it? The reverse is also common, where we treat the DLBCL and the FL comes back. A better understanding of the biology would give us greater insight.

- Race and ethnicity are also important factors, and consider resources such as the Anthony Nolan Registry from the UK. HLA has to do with race and ethnicity, and incidence is changing because there is an increasing Hispanic population that is predicted to change within the next 15 years.

- Dr. Morton: Some major themes that have emerged are, what and when do we measure, and how do we model it? If we could get into a specific biomarker or outcome, can we really thoughtfully address how that it is being measured and modeled? From study to study, it can profoundly change our interpretation of the results. I hope that some of these topics are inspiring to the senior investigators who have access to more resources and early career investigators regarding smaller, targeted studies that would be very reasonable.

Session II: Disease Biology and Novel Targets – *Steve Ansell, MD, PhD, Mayo Clinic, Rochester (Senior Investigator Grant Awardee)*

Dr. Ansell opened the second session by presenting his research grant entitled, "The Immunological Phenotype of Intratumoral T-cells in Follicular Lymphoma." Many T-cells are present in places where there are malignant cells, either scattered in or around the follicle. By better understanding T-cells, it may be possible to modulate their function, resulting in a better outcome. Location, phenotype, and neighborhood are key factors. CD4+ cell abundance (good) or paucity (poor) in the follicle impacts patient outcomes. When this information is incorporated into a FLIPI model (i.e., BioFLIPI), it adds to the prognostic relevance.[Mondello, 2021] Many cells present in the malignant follicle are Treg cells. In the absence of Treg cells, other CD4+ cells are able to make cytokines, but in the presence of Treg

Prognosis and Risk Factors Summary (Session I):

- Biomarkers for progression and transformation are lacking and may require using ctDNA and other technologies to account for the heterogeneity of disease, along with clinical trial partnerships to validate potential biomarkers. It is possible transformation is being missed at diagnosis, and a better understanding of the biology would provide greater insight.

- A consortium approach using existing data resources and application of information we have learned from other cancer types is needed to address gaps in identifying and integrating risk factor and prognostic data.

- An unmet need in patient care is aligning treatment with biologic, radiomic, and molecular genetic factors before a patient is treated, underscoring a critical need for development of prognostic, predictive, and surrogate markers.

- Smaller, targeted individual studies, along with the use of existing data resources and global collaborative efforts, should be leveraged to advance this aspect of the field.

- Debate exists between identifying patient populations who are going to perform well vs high-risk patients, as well as conducting risk-adapted vs response-adapted studies.

cells, the poorer the other cells function.[Yang, 2020; Yang, 2006] Of note, a TIGIT Treg cell is much more suppressive than other Treg cells. In FL, immune checkpoint therapy has been ineffective. TIM3+ and PD-1+ cells are much more likely to be exhausted. Thus, when PD-1 signaling is blocked, it is unknown which cells are influenced the most and how treatment affects the immune response.[Yang, 2012; Yang, 2019] Notably, cells that are both PD-1+ and LAG3+ are very suppressed and unable to make cytokines.[Yang, 2015; Yang, 2017] It does not only matter where cells live, but also which cells they interact with. Interestingly, CD4+ memory T-cells inside the follicles express CCR7, CD26, CD127, and CXCR3, and spend most of their time communicating with other T-cells.[Mondello, et al., 2021] This grant aims to investigate the different T-cell patterns in FL, understand the relevance of neighborhoods, and determine if they affect a patient's response and tumor growth. Dr. Ansell pointed out there are three general patterns: more T-cells, more B-cells, or an equal number of both. The T-cell populations that predominate differ, and it is important to understand how they regulate the immune system and tumor response. Aim 1 will involve transcriptomics to elucidate immunological neighborhood and function; Aim 2 will examine the impact on anti-tumor immune response; and Aim 3 will investigate if any cells play a role in regulating B-cell growth.

Panel discussion
Following the presentation, the floor was opened for comments and questions. The following points were raised by audience members for consideration:

- Paolo Strati, MD (M.D. Anderson Cancer Center): How do you plan to assess the role of monocytes and macrophages? What additional targets do you foresee being actionable to improve the activity of T-cells in FL?

  o Dr. Ansell: We found that there are different macrophages and some are SIRPα-low, high, and negative. We do not yet understand how these populations work, but they have a role in regulating T-cell function. In this work, we focus on T-cells, but there should be another project focused on macrophage function. We need to give T-cells an incentive to chase the tumor by activating the immune environment, or alternatively, diminish the T-cells, bring in fresh ones, and prevent those from being exhausted.

- Laura Pasqualucci, MD (Columbia University, Institute for Cancer Genetics) Does the genetics of the B-cells influence the different patterns in the tumors, and will this be investigated?

  o Dr. Ansell: This is another important variable that is not part of this focused analysis, but there is a lot of evidence suggesting that different genes and gene products have a significant impact on modulating the microenvironment.

- Dr. Chihara: What are your thoughts regarding the T-cell populations between newly diagnosed patients and those with relapsed disease? Do you think T-cell characteristics will stratify how we treat patients, particularly for R2-specific antibodies?

  o Dr. Ansell: Here, we have a snapshot at diagnosis, but I think your point is valid. These T-cell populations will change over time with treatment, and we are not sure how they will change, though I think changes will align with treatment choice.

Next, Abner Louissaint, Jr, MD, PhD (Massachusetts General Hospital; Senior Investigator Grant Awardee) presented the details of his grant entitled, "Interplay of Microenvironment and Epigenetics in a Novel Model of FL." The aims include to determine the relative impact of genetic alterations and microenvironment on FL cell survival and behavior; identify the main drivers of early progression and transformation in the context of FL clonal populations and microenvironment; and lastly, examine the interactions that can potentially be targeted with therapeutics. The main barrier to addressing these aims is the limited in vitro or in vivo model systems to assess them in real-time. To solve this problem, a patient-derived xenograft (PDX) model was created. Samples collected from patients with FL were implanted in immunodeficient mice. Histology demonstrated that tumors are composed of CD20+ B-cells and CD4+ T-cells, along with non-persisting follicular dendritic meshworks. A subset of mice experience transformation, in

which a well-circumcised mass becomes markedly invasive. Ultrasound-based technology was generated to detect tumors and transformation. The mice are monitored for engraftment, treated, and observed for tumor development. This PDX model will be used to define and characterize clonal populations and the lymphoma microenvironment in paired human FL samples and PDX models. The mechanism and role(s) of cross-talk will be defined in real-time through selective perturbation of the microenvironment in these models. Whole exome sequencing and single-cell DNA sequencing will be used to assess clonal populations and the TME. Additionally, spatial transcriptomics will be used to characterize the interplay between clonal cells and the TME, mainly using Slide-seq.[Rodriques, 2019; Stickels, 2021] Preliminary data demonstrate that the location of tumor cells can be identified, particularly in relation to structures (eg, follicles) and other cells (eg, T-cells, B-cells). These novel applications will be applied in various contexts of FL, including baseline samples in which primary FL will be compared with the PDX model, along with clinicopathologic correlation. Pre- and post-transformation PDX samples are being compared to further understand what differences exist among clonal populations and the TME. Lastly, the TME will be selectively perturbed; for example, CD4+ T-cells will be specifically depleted to determine if it provides a permissive environment for transformation.

Panel discussion
Following the presentation, the floor was opened for comments and questions. The following points were raised by audience members for consideration:

- Is this representative of human FL, given the high rate of transformation in the PDX model? If you would take a grade 1A or 2 sample, would they transform in the same way? The sample you showed is not a classical example— is this because you can engraft only specific samples? How fast will transformation occur? Eventually, it does not resemble what we usually see under the scope in human FL.

  o Dr. Louissaint: That is an excellent point, and it is true we do not have distinct follicles, as in human FL; however, we do see a nodular pattern. The dendritic meshworks that are part of FL do not persist in the model for a period of time, which may partially account for why we do not observe the tight follicles. At this point, this is still a good model because the cells resemble centrocytes and T-cells are present. Only a small subset of the cases may transform and the others can be propagated as low-grade FL.

- Michael Green, MD (M.D. Anderson Cancer Center): What is the engraftment rate, and are you going back to the tumors that do not engraft to compare the biology? Is it possible you are selecting for a certain biology in the PDXs themselves?

  o Dr. Louissaint: Initially, we try to generate three PDXs, and if they do not engraft, we will try again if we have more tissue. About 25% of samples will never engraft, and the remaining proportion will engraft, though propagation rate drops. Within the proportion that will engraft, about 1 out of 6 pieces of tissue implanted from the same patient sample will transform.

Building on this discussion, Laura Pasqualucci, MD (Moderator) presented the current gaps and unmet needs in the genetics and biology of FL. In FL, we observe de-synchronization of the germinal center (GC) B-cell program and *t(14;18)* is not sufficient to drive malignant drift.[Huet, 2018] FL and transformed disease arise through divergent evolution from a mutated CPC and involves additional factors that we do not yet understand. Malignant transformation of GC B-cells includes genetic alterations, epigenetic perturbations, and interactions in the TME, as well as interactions between the CPC and immune microenvironment. In order to make progress in FL, five major issues need to be addressed, the first of which is to understand heterogeneity. Aside from BCL2, mutations in epigenetic modifier genes represent a hallmark of the disease. Rather than a single-gene approach, a pathway-centric one needs to be taken, and these data need to be integrated, as none of these lesions individually has prognostic or predictive value at diagnosis. For drug development, clinically annotated large datasets need to leveraged, patients at diagnosis need to be uniformly treated, and comprehensive, multiomics data analyses need to be performed in order to identify the biological bases for FL subtypes related to early progression/relapse and high-grade transformation. Furthermore, liabilities of the CPC need to be identified and targeted, including vulnerabilities in CREBBP/KMT2D-mutant cells,

which represent early lesions in the evolutionary history of the tumor. Both methylation and acetylation are reversible modifications, and if lymphoma is dependent on these epigenetic perturbations, combination therapy using drugs directed at these axes could be used. EP300 is a potential liability in CREBBP-defective B-cells, which could be therapeutically targeted.[Meyer, 2019] Thirdly, it is critical to understand how genetic lesions or epigenetics instruct the TME to evade immune surveillance mechanisms and/or dependencies. Fourth, a better understanding of functional genetic interactions is needed, which may provide the basis for targeted, combination treatment (eg, functional interaction between CREBBP and KMT2D). Lastly, the non-coding genome should not be overlooked. In DLBCL, specific non-coding regions including mutations in super-enhancers prevent negative regulation by particular transcription factors, revealing yet another layer of genetics key to identifying novel targetable pathways.[Bal, 2021]

Ari Melnick, MD (Moderator) continued the session on disease biology and novel targets by emphasizing that an improved understanding of the mechanisms that drive FL is necessary in order to obtain a cure. Importantly, "one size fits all" is not an effective therapeutic approach for targeted or immunotherapies in FL. About 90% of patients with FL have one or more of the somatic mutations in the following chromatin modifiers, including EZH2, KMT2D, CREBBP, and/or EP300. The primary effect of EZH2 mutations is that B-cells become independent of T-cells, and instead, switch their dependencies to follicular dendritic cells.[Beguelin, 2020] Epigenetic clonal evolution drives FL progression and there is a need for novel epigenetic immunotherapy regimens for early-stage FL (eg, anti-FDC). In GC DLBCLs, epigenetic therapy can restore proper epigenetic programming, such as EZH2, HDAC3 and KDM5 inhibitors. [Mlynarczyk, 2019; Venturutti and Melnick, 2021] Animal models that accurately reflect the natural evolution and immunology of FL, along with an enhanced understanding of immune microenvironment patterns and evasion mechanisms are needed. In collaboration with Dr. Scott and others, Dr. Melnick has been working to characterize FL microenvironments using a 70-antibody panel through Hyperion imaging. Addressing community and organization in FL disease is critical, as demonstrated through intimate organization of different cell types and architectural layers, which is likely determining the immunological state of the tumors. Importantly, this can be studied in various bona fide FL murine models. It is unknown why CD8+ cells are unable to enter these tumors, though it may involve perturbations in immune synapses that occur when the epigenetic mutations are combined (eg, CREBBP plus KMT2D) as opposed to separate mutations. Dr. Melnick is investigating EZH2-mutant GCs, which form extensive FDC-rich meshworks.[Beguelin, et al., 2020] It is unknown why patients in trials respond to epigenetic inhibitors; thus, studying the potential of these agents on immune eradication of lymphomas may provide insight. In vehicle-treated murine models, no tumor growth was observed when treated with EZH2 inhibitors, illustrating the potential of these agents when used early to have long-term effects without continuous administration.[Takata, 2022] EZH2 inhibitors also induce an influx of CD4+ cells and granzyme CD8+ cells into lymphomas. Lastly, Dr. Melnick presented 3-photon microscopy technology developed by Chris Xu, PhD (Cornell University) that allows full thickness live imaging of lymphomas, which could be a very powerful tool for studying tissue dynamics.

Panel discussion
Following the presentation, the floor was opened for comments and questions. The following points were raised by audience members for consideration:

- John P. Leonard, MD (Weill Cornell Medicine): The clinical practical problem is really in the relapsed patient, despite wanting to cure everyone upfront. Should we focus our efforts on relapsed tissues, upfront, or both?

  o Dr. Melnick: I think the answer is both, since there is different biology and clinical unmet needs. Dr. Ansell: During treatment, there is a lot of variability, making it complex for researchers. If we first understand how the disease evolved, we can understand how to move forward. While we are all focused on the TME, we have to also look at the tumor macroenvironment. There are still a lot of things to understand and we are taking small steps at this point.

- Both in clinical practice and trials, we divide patients into early, stage, advanced stage, etc; do you think there are clinical categories are properly reflected by genetic, epigenetics, and TME specific changes? On the other hand, is it time to move away from clinical categorization and devise a biological characterization for clinical trials and practice?

- Dr. Pasqualucci: We do need to obtain a biological characterization, though the clinical aspects are intimately linked; therefore, if we had sufficient resources and tools to identify and correlate them, that would be ideal. In principle, we need to do both, but certainly biology will give us information.

- Dr. Melnick: We know a lot about biology, epigenetics, genetics, and microenvironment in ways that cannot yet be put into clinical practice, so it is frustrating to have the knowledge but not be able apply it because the technologies do not exist or we lack the biomarkers. We have to move to the point where we can use this information to guide patient selection, but it is not ready yet and the classification cannot yet encompass these data.

- Philippe Armand, MD, PhD (Dana Farber Cancer Institute): How do we prioritize the work in order to develop the best therapeutics? Is heterogeneity important for treatment selection, or can we focus instead on mechanisms of resistance, which may not be present at the onset of treatment? How can we get to effective, durable treatment for the majority of patients? Do we need to have targeted therapy in FL?

  o Dr. Pasqualucci: Companies conducting clinical trials may help us to address these questions. We currently do not know if it is something present at diagnosis or selected for during treatment, so again, we go back to the limited resources available in trying to elucidate this, though it is important. The LRF may be the setting to establish synergistic operative efforts.

  o Dr. Melnick: My hypothesis is that, this is not resistance but rather resilience, and we still need targeted therapy, either to the genetics, microenvironment, resilience, or all of those aspects together. Could resilience be dependent on genetic background, or it is a general property of cells? Many tumor types have the capacity to go into a resilience phase and acquire the potential to repopulate the disease afterwards, which could be an aspect in FL. We need to cure patients, not just put them in remission, and it remains possible that some of these niche considerations could remain relevant to cure.

    ■ Dr. Armand: When we analyze the initial tumor, we have no idea what that CPC is and how to target it, and if that is what ultimately drives transformation, it is the biggest risk to patients.

- Dr. Melnick: The animal models reflect the immunobiology of the tumors and may show us what the niche is.

  o Dr. Armand: Those animal studies may require us to study the cells that remain after treatment in addition to the cells that are at the onset.

    ■ Dr. Pasqualucci: ctDNA may help in this area.

- Dr. Smith: We frequently have people who transform, but we also have people where not only does the FL come back, but then they either have a second transformation or they go back and forth between the state of a very aggressive FL that behaves like a DLBCL. Then, no matter how often you perform biopsy, it is always FL, and they go back and forth between these two states. If we think about the population that really needs the most targeted therapy, it might be those people who bounce back and forth. Maybe this resilience concept is the key here, but what is known about the targets when something progresses, de-differentiates, etc?

  o Dr. Melnick: The B-cells in lymphomas are in a constant state of flux, which makes it difficult to determine which cells to target, or do you just target the underlying biology? FL is a unique disease because it arises from GC B-cells, which have the natural ability to go back and forth from centroblasts to centrocytes. Does the ability to return to centroblastic recycling what causes transformation, or is transformation something else that creates a more aggressive phenotype independent of that ability?

- Dr. Pasqualucci: It would be interesting to see if one of the roles of the epigenetic modifier genes is responsible for maintaining plasticity and allowing for constant re-programming of the tumor.

- Regarding the plasticity of cells, do you feel the CPC is in some way "locked" in a particular state because of the epigenetics? Or is it still something like a super-enhancer that is still movable and can spontaneously evolve?

    - Dr. Pasqualucci: We do not really have data to answer that question. If I have to speculate, I would think it is not locked in that state. Depending on the type of interaction with the immune niche, CPCs may acquire different genetic lesions in different geographical locations in addition to the initial events. We also know that cells within the tumor biopsy are very heterogeneous and may mimic certain aspects of different B-cell subtypes.

    - Is this contradictory to the fact that a couple of epigenetic mutations are the origin of the disease?

        · Dr. Pasqualucci: The epigenetic mutations are, in fact, not enough.

    - Dr. Melnick: Any of these epigenetic mutations are going to change the probability of the genome to have a certain chemical modification, but they are in constant flux, which is the nature of the genome, rather than being fixed. B-cells are normally chaotic and lymphoma cells even more so.

- There are dormant (rather than resilient) cells that do not respond to therapy, and eventually, they will progress. In my opinion, we need to learn how to target those cells because regular therapies are not effective and this may give a cure.

    - Dr. Melnick: In other tumor types, ATR inhibitors have been used to target resilient or dormant cells. It may be useful to refer to work by Constantine Mitsiades and Tim Ley focused on *MYC* in multiple myeloma and acute myeloid leukemia.[Delmore, 2011; Ferraro, 2019]

- Josh Brody, MD (Icahn School of Medicine at Mt. Sinai): Considering the epigenome is probabilistic and there is still some methylation with H3K4, if we could inhibit KDM5, we should get some trimethylation of H3K4. Therefore, is it true that there is still a decent amount of first methylation at H3K4, and is it a reasonable hypothesis to inhibit KDM5?

    - Dr. Melnick: This is a dynamic system, so loss of KMT2D or CREBBP is not sufficient to mediate significant loss of monomethylation or acetylation. These enzymes are in constant balance with each other, and with CREBBP, it is evident that the counteracting enzyme is mainly HDAC3.

- Dr. Brody: What is the side effect of too much H3K4? Would not every cell get hyper H3K4?

    - Dr. Melnick: You would think so, though it is remarkable how well HDAC3 inhibitors are tolerated. This speaks to the highly layered natured of the epigenome and compensatory ability of the cells.

- Dr. Pasqualucci: We always talk about these proteins as enzymes—while the enzymatic function is critical, we are increasingly understanding that both CREBBP or KMT2D encode non-enzymatic functions that may be contributing an additional level of complexity. For example, it could be the cause for why truncated mutations are different from missense mutations, and we need to examine that.

- Dr. Brody: If KMD5 inhibitors did not work, you might try a KDM1A degrader.

    - Dr. Melnick: Knocking down KDM1A is not sufficient to inhibit enzymatic inhibition of H3K4. Only in certain situations would it have a high responsiveness.

Dinner Discussion – *John P. Leonard, MD (Weill Cornell Medicine; Speaker)*

Following dinner, Dr. Leonard outlined three goals concerning treatment of patients with any malignancy; namely, to cure patients, extend survival, and maintain or enhance QoL. One main consideration in FL is if some patients are

being cured, and if so, what proportion of them are being cured and how does treatment selection influence cure? A second consideration is that, aside from the addition of anti-CD20 to chemotherapy, there is little evidence that specific therapy choices extend OS. Thus, the focus should be on QoL. It is important to not make assumptions as during discussions of therapy choice with patients and to determine their goals. Dr. Leonard presented hypothetical curves in measuring QoL in a single-arm FL study. Often, the study begins with 100 patients, and over that time, progression-free survival (PFS) goes down, and patients that progress go off-study. At this point, QoL is being measured on those patients that remain on the drug, with no control group, and there is minimal data on the majority of patients who go off the study drug. Thus, there is no QoL data from the majority of patients at the end of a clinical trial, and ultimately, it is limited by time. Similarly, in a hypothetical randomized FL study, assuming a difference in PFS and OS is same, QoL is measured. However, there will be a loss of patients, with no QoL data from the majority of patients, and comparisons between arms do not account for those patients who progress. Overall, there is a lack of robust data concerning QoL for FL patients. Physicians make assumptions and/or considerations about an individual patient's treatment and QoL, including how the intensity of treatment relates to disease-free survival (DFS) and PFS (eg, rituximab vs rituximab + chemo). Other considerations include how the toxicity of treatment compares with the "toxicity" of disease or reoccurrence, and weighing the pros and cons of maintenance treatment. Psychological and financial issues, age, monitoring (eg, more vs less scans), and long-term treatment-related risks are also factors.

Disease Biology and Novel Targets Summary (Session II):

- There should be a project focused on studying differences in macrophage populations and another exploring how genetic patterns of B-cells may influence tumors.

- A need still exists for animal models that reflect the true nature of tumor tissue as well as cell lines that reflect modern treatments. A repository is needed to increase access to such viable models and cell lines across institutions.

- Clinically annotated datasets need to be leveraged to pinpoint the underlying biological basis for different FL subtypes, allowing for an improved understanding of disease heterogeneity and the development of targeted drugs (eg, targeting vulnerabilities in CPC, epigenetic drivers, and non-coding regions).

- Clinical classification of tumors needs to incorporate biological and clinical aspects, yet there remains a need for resources and tools to identify and correlate these data.

- In terms of targeted therapies, some debate exists on directing treatment strategies towards disease heterogeneity vs mechanisms of resistance/resilience vs dormant CPCs (or a combination of approaches).

If 80% of patients will not die of their disease, then QoL is the dominant issue that should drive their therapy. QoL is the largest unmet need where there is not enough research and funding. In fact, development of new tools could lead towards more precision QoL-directed therapy. Dr. Leonard concluded with open-ended questions, including consideration of using PFS endpoint in FL studies; ways in which QoL assessments can be improved with varying regimens, particularly regarding confounders during comparisons; and how to apply more rigor during data collection in clinical trials as well as in routine patient care.

Panel discussion
Following the presentation, the floor was opened for comments and questions. The following points were raised by audience members for consideration:

- For patients on rituximab, is maintenance a good choice for them related to PFS, especially as it is related to COVID-19 and QoL? Do I really want them to go to a hospital with pneumonia? My reflection is how is COVID-19 related to QoL landscape.

- QoL improves if you meet or exceed the requirement for the age- and sex-matched population, which is patient-reported. A key contribution of the Foundation was a toxicity commission in hematology led by LRF Scholar Dr. Gita Thanarajasingam.

- We are living in a country with patients with varying socioeconomic status (SES), and I perceive these differences enormously. QoL should take into account the SES aspect and adds an additional layer of complexity.

- QoL is very dynamic, much like the TME—we only have a snapshot and it can vary day to day. How can we measure QoL continuously rather than take a questionnaire every few months? We have assumptions that patients are answering with honesty. If they were aware of the fact that whatever they fill can drive change in treatment, they may start to be more concerned with how they answer.

  o Dr. Leonard: I agree that the questionaries can be subjective. We should be following QoL over time in a rigorous patient-reported outcome (PRO) to correct for variability.

- How do we apply precision QoL when we have patients with differing low- and high-grade tumors? Can we leverage all randomized clinical trials (RCTs) that have QoL data?

- Considering disease heterogeneity, is there something we can do to prospectively design and collect QoL data in a longitudinal way? PRO CTA and other measures? Is there a movement to understand QoL across disease heterogeneity and collect this data?

  o The patients who will go on CAR-T cell will be different than those who will receive frontline rituximab, so the challenge is how to normalize for the disease and/or treatment there. Ideally, we would be able to at least correct or account for that.

    ■ Are there some concerns that are universal, despite treatment, that are intrinsic to having FL, or are there some that are specific to disease and treatment?

- Many questions remain, but perhaps we should start with LRF developing tools to measure QoL, financial, and toxicity aspects across different populations. Perhaps there should be a mandatory tool for every study we do for a set of basic QoL aspects.

- It is difficult to understand the personality of a person if they are new patient, so it is a challenge to make that assessment quickly. Is there a way to find out this data, perhaps through a psychological assessment? Additionally, there are many approved treatments in the relapsed setting that are not necessarily compared with each other. We are not sure how to sequence them, so we should have studies that allow for different treatment sequencing and figure out how QoL is affected.

- QoL can be normalized for other variables, but the most important concept is that QoL is a continuum, and it is critical to continuously measure it when a patient is on and off treatment and in remission over a large population. For example, for those patients that we tell to "watch and wait"—it is really "watch and worry" and those patients will have a different QoL. We need to be able to measure across the continuum and then analyze across variables, including SES and on/off treatment, then we will get a better idea of FL burden.

  o Expectation setting and patient education are important for making sure those "watch and wait" patients are educated to ease QoL. Secondly, subsequent therapies will also affect QoL, and we need to capture those data.

- Perhaps we could give patients devices to measure symptoms on a daily basis (eg, smartphone and smart watches), or something similar to see how QoL changes on a particular treatment.

- QoL is not static—it is a chronic journey and how you frame it from the first time you meet the patient is critical. There are differences I have noticed in patients that I have inherited compared with those that I first diagnosed because the disease and/or treatment was framed differently. It is on us as physicians from day 1 to make sure we are framing it appropriately to preserve QoL.

- We need to precisely separate the different issues from a research perspective, and then we need to quantify the risks and benefits. This contrasts with earlier talks in terms of integrating data.

- This is a complex, two-folded issue. Each of us will view QoL very differently. Some components can be measured quantitatively, but then there are others that are subjective, adding to the complexity. However, we have people at universities who are specialists, and we need to involve these specialists who are assessing these types of data.

- QoL data needs to be collected in real-time. We have population norms and populations with other chronic diseases that might help us triangulate diseases. We should build this into trials, though it will require a thoughtful framework.

- One part of the uncertainty is the state of the patient at time of diagnosis. Could QoL change when we have better prognostic markers?

- QoL is under-studied, under-measured, and under-accounted for among everything we do for patients with FL. It should be part of the LRF initiative to solicit proposals, gather experts, and devote funding and effort in this direction. As pointed out, we need to make sure we have the right people in the room, and this is a very clear way for how we can make a big impact for patients.

Session III: Transformed Disease - *Ranjana Advani, MD, Stanford University School of Medicine (Moderator)*

Dr. Advani presented a summary of the Transformed Lymphomas Scientific Workshop held in August of 2021, the findings of which were published in a white paper distributed to audience members. The rarity of transformed disease is one of the greatest challenges, and it can only be addressed through multi-stakeholder collaboration and shared scientific resources. A task force and a mini symposium in conjunction with the FDA are needed to address clinical trial issues and drive sustainable change. Transformation is primarily a genetic event combined with epigenetic and microenvironment changes, including *CREBBP* and *KMT2A* mutations. Additional research is needed to improve the sensitivities of detecting abnormalities and predict those patients that will progress to tFL. Both histologically and clinically, there is a lack of population data regarding tFL subtypes. While independent risk factors have been identified, they do not adequately estimate the risk of transformation and have not been integrated into clinical practice. One way to overcome the barrier of limited biopsy samples is to use ctDNA; however, a considerable gap exists in translating this data into being useful for predicting transformation and reliable models are lacking. Most guidelines for tFL are based on expert opinion without optimal evidence, including those issued by the National Comprehensive Cancer Network (NCCN). Dr. Advani pointed out that the areas identified for further research regrading biology and prognosis included biomarkers, imaging correlative, and creating a biobank, perhaps with the assistance of the LRF. A better understanding is needed regarding how prior therapies impact the disease and subsequent treatment. More

real-world evidence is needed, along with increased patient access, strong collaboration, and impressing upon drug companies and regulatory bodies that tFL is an area of unmet need. The FDA may use a single-arm phase 2 trial to support approval if the agent has both high overall response rate (ORR) and duration of response (DOR), though toxicity is a high consideration given the PI3K inhibitors. The FDA noted that modified or unique response criteria would require discussion as well as data to show that the new criteria translate into clinically meaningful benefits to patients. Dr. Advani concluded by proposing open-ended questions for audience members to consider in the context of LRF, including the most impactful biological and clinical questions to address relevant to upcoming Jaime Peykoff awards; how to overcome rarity issues; and the possible need for a clinical trials tFL consortium.

Patient Outcomes and Quality of Life Summary (Dinner Discussion):

- In clinical trials, there is a lack of robust data regarding QoL for patients with FL. As this is an increasingly important aspect of patient care, there is a need for well-designed, rigorous QoL data collection and tools, both in clinical trials and routine patient care.

- QoL should be followed continuously and in real-time rather than via static snapshots, which requires more carefully designed clinical trials and rigorous PROs.

- LRF could assist with developing tools to measure and normalize QoL across different patient populations and perhaps make QoL data collection a requirement for future studies.

- QoL studies should be aligned with treatment type and/or treatment sequencing.

- Collaborations are needed with specialists to collect and analyze quantitative and subjective QoL.

- LRF should solicit proposals, gather experts, and direct funding towards measuring and improving QoL.

Next, Brian Link, MD (Moderator) explained how no Jaime Peykoff grants were awarded to proposals on tFL during this funding cycle. He emphasized that the primary goals of the following discussion are to identify strategies to decrease the burden of tFL and devise solutions for infrastructure mechanisms in collaboration with the LRF that could be leveraged to overcome some of the obstacles to studying tFL (eg, biology and infrequency).

Panel discussion:
Following the presentation, the floor was opened for comments and questions. The following points were raised by audience members for consideration:

- Dr. Smith: Should we have a master protocol for marginal zone tFL and Richter's Transformation, or do we continue to keep them in different boxes?
  - o Dr. Link: In my opinion, these diseases should not be categorized together for management strategies, but there could be some commonality with early detection tools.
  - o Dr. Smith: I agree that we cannot have master protocol for transformed disease. Additionally, we should have the LRF organize a consortium on clinical trial design.
- Basically, we are dealing with two clones—one that is more sensitive to chemotherapy and the other is not. Many times, it is responsive to radiation and that is why the combined modality approach is limited, which is something to take into consideration. Given the rarity of cases, from the clinical aspect, why not lump these two together?

- Dr. Armand: Perhaps the solution to treating tFL is to approach it from the perspective of large cell lymphoma and see if there is any value to treating different subsets. Namely, at the onset, how do we not miss transformation? It has high clinical relevance, and when we miss it and treat those patients with bendamustine, we really cause them harm. There must be a way to use ctDNA to figure out if they have a transformed clone somewhere and treat them differently.

  - Dr. Link: There must be a way with ctDNA to detect pre-clinical transformation—that would be the holy grail. Does this potential exist now, or does it more require targeted research? Also, does this genetic classification lead you to think that transformed lymphoma is really a dynamic process, or is it really that some people have FL, some have DLBCL, or do they have a third disease that sometimes appears follicular and other times diffuse?

    - Dr. Armand: Since the classification is so new, there is much we do not know, including questions revolving around plasticity. It seems to me we have a better chance at approaching this problem from the heterogeneity of large cell lymphoma rather than developing a consortium solely on a transformed lymphoma where we will miss half of the cases. I think we have the tools to do this research (eg, CAPP-Seq).

- Nilanjan Ghosh, MD, PhD, (Levine Cancer Institute at Carolinas HealthCare System): Before we get to ctDNA in the real world, is there a way we can use existing technology to disseminate information, with or without a biopsy to come up with algorithm to get predictability at baseline to treat them more appropriately?

  - Dr. Link: What would be the threshold in terms of percent transformation to change treatment strategy?

    - Dr. Ghosh: When there is a clinical suspicion for transformation, we lean towards R-CHOP.

- Dr. Link: If you had an algorithm based on retrospective, real-world data that predicts for transformation in BR-treated patients, but does not predict for transformation in R-CHOP-treated patients, does it then become a predictive biomarker algorithm?

- Dr. Lossos: Is transformation one process, or are there many processes that lead to transformation? Studies have demonstrated that multiple processes are involved and it is not a single mechanism. Does the clone already exist or not? If so, how can we apply ctDNA? We published that there are two main expression patterns, namely, upregulation of MYC and secondly, downregulation of MYC and its target genes, though no specific mutation explains these two patterns. Do we diagnosis it correctly? No, because the frequency of transformation depends on method used; thus, we are probably missing transformation in many patients upfront. Having a pool of specimens is problematic because the majority of biopsies are core biopsies, which can create storage problems. There would be Institutional Review Board (IRB) problems for transferring specimens, and it is possible that transformation would be missed in the sample. Regarding marginal zone lymphoma, genetic similarities are unlikely.

- Dr. Salles: The complexity of the questions does not mean we should not address them. Referring to the Vancouver paper, even with ultra-deep sequencing, the mutation present in transformed lymphoma in a substantial number of cases were not detectable. Given all the heterogeneity, we should not lump all these patients together when talking about FL. The observation with bendamustine is not completely new, and even with other treatments, we have seen transformation occur. T-cells might be important for some cases, which may need to be addressed.

- John Timmerman, MD (UCLA Oncology Center): We need a muti-center repository of specimens that includes core biopsies or preferably large biopsies, but also some samples that are dedicated to establishing novel cell lines. We need the cell lines to reflect transformation now—not 20 or 30 years ago. We want early-passage cell lines that reflect the recent disease biology and evolution within our modern therapies. We could then test new drugs and mechanisms of resistance.

- o Dr. Link. This is a great argument. It could be an obstacle to create a physical tumor bank because of IRB issues. Though, if we could agree upon a common way to interrogate these and create a common dataset process, it could be a partial step forward.

  - ■ Dr. Timmerman: We have a HIPAA-compatible tissue lymphoma bank and there is a standard operating procedure that if you de-identify the samples, they can be shared outside. There could be a virtual model where you share the data, but there does need to be more of a coordinated effort needed here to share resources and one easy way to do that would be to share cell lines.

- Dr. Pasqualucci: The limit is that there are no unifying genetic lesions for transformation. Because there is no evidence of the transformed clone at diagnosis, ctDNA to monitor clones would not be applicable. Unless we can eliminate the sitting cell and recognize it, we will be limited. There is a lot going on in the non-coding genome (eg, MYC positive cases and super-enhancers), and this should be an area worth exploring. One major difference between FL and tFL is the mutational load and somatic hypermutations, which also needs to be explored.

- Thomas Habermann, MD (Mayo Clinic, Rochester): From a clinician's perspective, I had a recent case where four biopsies appeared to be low-grade and follicular. Someone sent it off for FISH and there was a *BCL2 MYC* rearrangement, and on a PET scan, the SUV was 25 on a 12-cm mass, which was not low-grade disease. Firstly, what is that disease? Secondly, how do we define transformation clinically vs pathologically. I would like to see a definition, as there is some difficulty deciding what is a transformation if it is not pathologically defined.

  - o Dr. Link: Although it underrepresents the reality of transformation, I think we need to study histologic transformation. The question I have is, does it have to be sequential? Is concurrent diagnosis of FL and DLBCL the same entity, and does that expand the opportunity to study this problem compared with sequential diagnosis?

  - o Dr. Habermann: I think both should be included. The literature shows that FL with 1% to 2% of patients have *BCL2 MYC*.

    - ■ Accumulating evidence shows that *MYC* translocation detected by FISH does not necessarily indicate aggressive course in FL.

- Chelsea Pinnix, MD (M.D. Anderson Cancer Center): For any repositories, we need to think about banking radiographic data, even if we are not analyzing it now. We need to collect PET scans in a separate repository from initial diagnosis to biopsy as well as contrasted CT scans. We might not be able to interrogate all that data now, though it could be helpful in the future.

  - o Dr. Link: Have you or your team had success in compiling muti-institutional nuclear medicine studies? An early obstacle we have faced is de-identifying patient-specific identification.

    - ■ Dr. Pinnix: Yes, and you have to get right personnel involved to de-identify. Also, you need to ensure that they are standardizing PET scans, etc across institutions. There are challenges, but these tools are sophisticated and can be leveraged for later use.

- From a genetic perspective, we cannot distinguish between DLBCL and FL, but it may be important to combine the two diseases for clinical trial purposes from a pathological perspective, especially considering evidence that there is underlying FL.

- Dr. Smith: Regarding having shared resources, is there interest in having a clinical data commons for transformed lymphoma?

- Dr. Lossos: This disease is a spectrum with a leukemic phase. I would not make a diagnosis of DLBCL based on a *MYC* translocation unless there was evidence of large cell involvement.

- One would argue that the answer to all our question is biology, biology, and biology. We all need to become biologists. We are underutilizing what we already have regardless of what is still unknown (eg, p53). We need more rigor in research. For example, we need to figure out how why the BCL2 inhibitor does not work in FL, but does in AML, which could reveal a fundamental genetic event.

- Dr. Advani concluded the session by summarizing the major themes, including creating an image bank; novel cell lines; data commons; treatment based on what we already know about biology; developing predictive models; threshold for treating people differently if we knew they would transform; examining non-coding lesions; and not all mutations are equal.

Session IV: Building on Recent/Novel Proof of Concept Treatments - *Hans-Guido Wendel, MD Memorial Sloan Kettering Cancer Center (Senior Investigator Grant Awardee)*

Dr. Wendel started the session by presenting the three aims of his project, entitled "Understanding and Therapeutically Targeting Epigenetic Drivers of Oncogenesis and Immune Evasion in FL." Aim 1 is led by Dr. Salles with the goal of identifying clusters with specific vulnerabilities and exploring clonal evolution among serial clinically annotated samples. Aim 3 is led by Santosh Vardhana, MD, PhD (Memorial Sloan Kettering Cancer Center) and is focused on uncovering the role of methyltransferase mutations in FL immune surveillance. Dr. Wendel's presentation centered on Aim 2, which explores the interaction between *KMT2D* and *SETD1B* mutations and therapeutic strategies. *KMT2D* is the most frequently mutated gene in FL.[Ortega-Molina, 2015] *SETD1B* (or *KMT2G*) is the *H3K4* tri-methylation mark and there is some debate if that mark has a function or not. *SETD1B* has mutations in both FL and DLBCL that occur across the coding sequence and are consistent with a loss of function. In FL, the *SETD1B* mutations always occur with *KMT2D* mutations, suggesting that the events might be cooperative with regard to disease development. Using a murine model, *SETD1B* was shown to be a tumor suppressor and to cooperate with *KMT2D* loss in FL. Based on histology, the loss of *SETD1B* likely alters lymphoma behavior, allowing for a slightly more aggressive, though not transformed disease. Interestingly, *SETD1B* was identified with other known venetoclax-resistant genes in a CRISPR screen. The loss of *SETB1D* impairs the response to venetoclax in vivo, and in isogenic cell lines, *SETD1B* does not affect *BCL2* and MCL1 expression. Dysregulation of *p53* pathway genes and regulators seem to be the effect of losing *SETD1B*. In the *SETD1B* clone, the loss of *H3K4* tri-methylation is most pronounced at promoter elements (43%), with the *p53* pathway being among those affected. Loss of *SETD1B* attenuates BH3-only proteins; thus, *SETD1B* may have a role in making the *BCL2* gene unnecessary. Using a *KDM5* inhibitor restored sensitivity to venetoclax in *SETD1B*/*KMT2D* mutant *LY19* cells, which may be an epigenetic way to augment sensitivity to cell death induction and may affect other treatments. In over 200 FL samples, *SETD1B* and *p53* are mutually exclusive and statistically significant. In nearly 250 DLBCL samples, they are almost completely mutually exclusive. *SETD1B* loss can partially replace some of the functions of *TP53* inactivation in FL and DLBCL. Through this research grant, Dr. Wendel and colleagues will explore whether *SETD1B* directly interacts with *TP53* or if it is epigenetic, and determine the efficacy and safety of venetoclax/KDM5 inhibition.

Panel discussion
Following the presentation, the floor was opened for comments and questions. The following points were raised by audience members for consideration:

Transformed Disease Summary (Session III):

- LRF should organize a consortium to address issues with clinical trial design for tFL.

- A considerable gap exists in translating data collected via ctDNA to be useful for predicting transformation, and reliable models for tFL are lacking.

- There is a need for evidence-based guidelines for the best management of sequentially tFL disease.

- Debate exists regarding whether or not to combine marginal zone tFL and Richter's Transformation.

- A multi-center repository of specimens that includes core needle or larger biopsies and samples dedicated to establishing novel cell lines are needed. Repositories should also include clinical and radiographic data.

- Creating repositories may require a coordinated effort to develop a common dataset process to help address IRB issues and will require the proper personnel to de-identify data.

- A potential project worth exploring is examining the non-coding genome in tFL, as well as the mutational burden differences between FL and tFL.

- There is no genomic change in *H3K4* tri-methylation, therefore, why is this gene affected and not the other ones, and could they be partners? *BCL2* is being inactivated or unnecessary in this setting. What are the other mechanisms that can potentially replace the function of BCL2?

  o Dr. Wendel: There may be in vitro assays that can reveal mechanisms specific to page 53 to tease out those connections. Regarding the failure of venetoclax, there may be epigenetic lesions that make these tumors no longer dependent on BCL2, and this is where KDM5 inhibitors could be interesting for restoring apoptotic sensitivity.

    ■ These cells are still not dying; thus, some compensation may be occurring.

- Dr. Pasqualucci: Are the tumors in mice IRF4 positive? Could this reflect particular subgroups of FL? Secondly, could humans have these mutations?

  o Dr. Wendel: The cells are B220 positive.

Next, Andrew Zelenetz, MD, PhD, (Memorial Sloan Kettering Cancer Center, Moderator) summarized molecular targets in FL while highlighting some of the limitations and challenges to drug development. Continual clonal evolution is inherent to FL,[Devan, 2018] and there are numerous targets in FL and tFL with both recurrent translocations and mutations.[Devan, et al., 2018] Dysregulated BCL2 expression arising from *t(14;18)* is observed in 90% of FL cases. The mutations in epigenetic modifiers have a vast impact on multiple tumor intrinsic and TME factors that alter the growth and regulation of FL.[Devan, et al., 2018] *EZH2* is an epigenetic regulator of gene expression and required for normal B-cell biology in the GC.[Beguelin, 2013; Gan, 2018; Morschhauser, 2019] Approximately 20% of patients with FL have *EZH2* gain-of-function mutations.[Bodor, 2013] Tazemetostat is a selective inhibitor for EZH2, affecting enzymatic activity of EZH2 in both wild-type and mutated cells.[Italiano, 2018; Morschhauser, 2017; Morschhauser, 2020] Theoretically, FL should be cured by targeting BCL2; however, BCL2 is part of a large family of interacting pro- and anti-apoptotic proteins.[Kale, 2018] BH3 profiling has demonstrated limited dependence of FL on BCL2 as well as MCL1; however, there is significant co-dependency of BCL2 and MCL1, and data suggest combinations of venetoclax with MCL1 or PI3Kδ inhibitors should be further investigated.[Rys, 2021; Serrat, 2020] Dr. Zelenetz emphasized that

there are numerous undruggable targets, which could be addressed using novel approaches such as proteolysis-targeted chimera (PROTAC). BCL6, MYC, Ikaros/Aiolos, and EP300 are potential targets amenable to PROTACs.[Bekes, 2022] CREBBP and EP300 are both histone acetyltransferases important in B-cell biology, and when CREBBP is diminished by mutation, overexpression of BCL6 acetylation and under-expression of p53 acetylation alters biology. [Green, 2015; Jiang, 2017; Pasqualucci, 2011; Zhang, 2017] In a clinical trial using the HDAC inhibitor mocetinostat, responses were poor in a select group of patients with CREBBP mutations, and the study was discontinued for futility. An alternative mechanism is to create a synthetic lethal mutation by knocking out EP300 using PROTAC, which has less toxicity on wild-type cells than on CREBBP mutant cells.[Meyer, et al., 2019] Lastly, Dr. Zelenetz focused on PI3Kδ inhibitors[Huet, et al., 2018; Serrat, et al., 2020], indicating that toxicity was a limiting factor in clinical trials of idelalisib, copanlisib, duvelisib, and umbralisib.[FDA, 2022] While PI3K is a validated target and multiple agents have shown favorable response rates and highly favorable PFS, the drug dosing and schedules may not be optimized. Intermittent dosing with the novel PI3K inhibitor zandelisib resulted in lowered toxicities, with response rates of up to 70% in patients with and without a history of POD24.[Pagel, 2021; Soumerai, 2018; Zelenetz, 2019] Moving forward, novel trials need to identify the optimal dose and prospective integrated safety databases are needed to identify toxicity signals early in drug development.

Catherine Diefenbach, MD, (NYU Langone Health, Moderator) continued the session beginning with an overview of the Checkmate 104 study.[Armand, 2021] While checkpoint blockade is ineffective for most patients with FL, it sensitizes patients with R/R non-Hodgkin lymphoma to subsequent therapy, and this raises the question if the checkpoint inhibitor is having an effect on the stromal environment or the TME irrespective of clinical response.[Carreau, 2020] In contrast, the BiTEs, such as mosunetuzumab, seem to work extremely well in FL.[Schuster, 2019] There are key differences between inflamed TME (eg, Hodgkin lymphoma) and non-inflamed lymphomas (eg, FL, DLBCL) as they related to therapy.[Kline, 2020] In an inflamed TME, it would be ideal to augment T-cell activity, whereas in a non-inflamed TME, BiTEs could bring T-cells into the TME and turn it into an inflamed one. LAG-3 expression differentiates exhausted vs functional PD-1+ T-cells, and patients with FL with increased LAG-3+ T-cells in the TME correlates with poor outcomes.[Yang, et al., 2017] CD8+ T-cells expressing KLRG1 enter a cell death pathway whereas those expressing KLRG1 but not CD27 differentiate into memory cells.[Wu, 2021] T-cell phenotypes correlate with patient outcomes (eg, CD8+ T-cells lacking expression of both KLRG1and CD27 are associated with poor event-free survival and OS in patients with FL).[Wu, et al., 2021] Treatment of CD8+ T-cells with a PI3K inhibitor downregulates transcription factors required for CD27/KLRG1 differentiation. Importantly, this type of information on immune evasion mechanisms can drive personalized therapy. If a patient's biopsy reveals they have terminally differentiated effector cells, treatment with a PI3K inhibitor may affect the outcome. Additionally, Dr. Diefenbach showed that the gut microbiome of patients with FL is significantly different than control patients, and pretreatment diversity and composition can predict treatment response.[Diefenbach, 2021] Assessing immune infiltration can give insight into patients who are at risk for POD24; however, it raises the question of the degree of heterogeneity of POD24 as it relates to immune signatures and outcome prediction.[Tobin, 2019] Lastly, Dr. Diefenbach reiterated that the challenge of predicter biomarker discovery is rooted in heterogeneity and is both genetic and spatial. Multiple in-depth genetic analyses have been unable to identify a single unifying driver of transformation. Lymph node stromal cell transcriptional plasticity may play a key role in understanding alterations associated with specific patient outcomes.[Mourcin, 2021] Fibroreticular cell transcriptional subtypes correlate to different OS outcomes, and FL myeloid-derived suppressor cell abundance is a predictor of OS.[Park and Klairmont, unpublished data] She concluded by emphasizing the importance of therapy sequencing and understanding biology to drive personalization, and she proposed that biologic signatures, if validated, could be more than prognostic factors and instead novel therapeutic targets.

Panel discussion
Following the presentation, the floor was opened for comments and questions. The following points were raised by audience members for consideration:

- Dr. Zelenetz: How do we sequence therapies considering the heterogeneity of disease at relapse? Moreover, how can we get to the questions to optimize drug therapy?

- Dr. Melnick: Currently, there is a disconnect between what we know about FLs and the patients. We know very little about the biology of these tumors, and therefore, we do not know the targets. We need to apply new knowledge and technologies to tease out the details of the tumor biology. It is imperative to understand the biology, but one limitation and a major unmet need is the lack of model systems that reflect the full nature of the tumor tissue. He referred to the importance of Dr. Louissaint's research and his PDX model, which could be shared across the field. Dr. Melnick also referred to adoptive transferable cells made from his lab group derived from various genetically defined FL cells, which his group is sharing to anyone across the field. He emphasized the importance of developing and sharing such models to more effectively collaborate.

- Dr. Cheson: Regarding the tazemetostat study, the ORRs of patients with wild-type and mutant *EZH2* do not match (35% vs 69%, respectively).[Morschhauser, et al., 2020] Our group has a propensity-matching analysis of that study in press showing that the ORRs are actually very similar and the PFS curves are superimposable, which raises the issue of how a drug really works. Additionally, we can learn a lot from the umbralisib trial.[Fowler, 2021] If we examine the widening hazard ratio (HR) as a result of COVID-19 deaths, we see that the control arm completed therapy before the pandemic began and the study arm continued indefinitely. This raises the question of cognizant study design in the time of COVID-19. We have to carefully evaluate the dose, dosing schedule, and perhaps take a retreatment approach rather than indefinite treatment. Furthermore, clinical trial development needs to be clinically and statistically planned taking into account COVID-19.

  o Dr. Zelenetz: The COVID-19 pandemic has accentuated and significantly magnified the risk of continuous therapy that depletes the immune system.

    ▪ Dr. Cheson: If you remove the patient deaths due to COVID-19, the HR is less than 1; therefore, the drug was good but the pandemic has damaged the clinical trial process. I agree not to give drugs indefinitely, and instead, take a proactive stance against COVID-19 with patients on B-cell-depleting drugs

- Despite clinical differences, BCL-ABL and BCL2 are hallmarks of disease and should continue to be targets, as biology is the underlying cause and, as Dr. Diefenbach showed, may have an impact on sequencing. Similarly, studies of cyclin D1 in mantle cell lymphoma show that pre-clinically, it is a target and single agent therapy is ineffective, but when in combination, it is more effective.[Wang, 2020] Regarding immunotherapy, we should think not only of what the target molecule is, but what is causing expression of the target and research how to enhance immunotherapy using that approach.

  o Dr. Diefenbach: Understanding what these therapies do to the TME is going to be critical to understand how to sequence therapy or the impact of a therapy on subsequent ones.

- Dr. Chihara: Taking into account the PI3K inhibitors, should we change the clinical trial design in early phase? Is there an appetite for LRF and the group to combine phase 1 clinical trial data within the last 10 years to create a database and to better understand and prioritize factors for future drug development?

  o Dr. Zelenetz: One of the problems with the PI3K inhibitors is that the early signal was quite favorable and even in RCTs, PFS and HRs were good. It was the cumulative late toxicity that was the issue. I think what we need is not just disease characteristics but also more about state of the patient. Are there early measures that we can identify of late toxicities? How early in drug development can we have insight into late toxicities? If we could determine late toxicity signals from clinical trial data on based on patient characteristics and other parameters, that would be very interesting.

- Eduardo Sotomayor, MD (Tampa General Hospital Cancer Institute): The TME is important for context in the frontline vs relapsed settings; thus, we need to be careful when describing the ineffectiveness of checkpoint inhibitors, as some studies have shown excellent outcomes. As a group, we need to think more about neoadjuvant immunotherapy as TME is more favorable in that situation compared with the relapsed setting.

Session V: Emerging Treatment Strategies - *Dr. Todd Fehniger, MD, PhD, Washington University in St. Louis (Senior Investigator Grant Awardee)*

Dr. Fehniger began the session by presenting the details of his grant entitled, "NK Cell Biology and Therapy for Follicular Lymphoma." Natural killer (NK) cells protect us from infection and cancer and are a founding member of innate lymphoid cells. They differ from T-cells in that they do not have recombined DNA for antigen-specific activating receptor, and instead use germ-line DNA encoded inhibitory and activating receptors that are tuned by cytokine receptors. NK cells perform similar functions as CD8+ T-cells, exhibiting cytotoxicity activity through granzymes and perforin as well as producing cytokines and chemokines. The dynamic interaction of NK cells with self-cells via MHC class I receptors is altered in malignant transformation, often resulting in loss or downregulation of MHC class I which releases the brake on NK cells and allows these cells vulnerable to attack. Few studies have evaluated NK cells in patients with FL,[Enqvist, 2019; Fehniger, 2003; Klanova, 2019; Landskron, 2014] and one challenge is that they often require specialized multidimensional data analyses. Dr. Fehniger's group has designed multidimensional panels to deeply assess NK cells in the TME of FL. One aim of the grant is to define the phenotypic and functional status of NK cells in patients with FL, including the TME. This will be accomplished in part by applying multidimensional analyses to a number of samples from a phase 1 clinical trial of an IL-15 drug (N-803) plus rituximab in patients with FL as well as the WashU lymphoma bank (>100 FL patients).[Foltz, 2021] In samples from patients treated with N-803 plus rituximab, NK cells become predominate in the tumor. The second aim of the project centralizes around the development of CAR memory-like NK cell therapy for FL. Memory cells have enhanced anti-tumor function via increased activating receptors and have shown to be safe.[Berrien-Elliott, 2020; Berrien-Elliott, 2022; Gang, 2020; Romee, 2016] Also, memory NK cells have enhanced mAB directed response (ie, CD16), and memory-like differentiation increases antibody-dependent cytotoxicity.[Becker-Hapak, 2021; Wagner, 2017] Additionally, CAR-modified NK cells exhibit potent responses to NK-resistant lymphoma.[Gang, et al., 2020] This grant is focused on advancing these findings in the clinical setting and exploring questions, including discovering if dual-targeting with CD19/CD20 or if TGF-β blockade will enhance responses.[Yang and Ansell, 2012] The grant will also enable an IND application and inform initial phase 1 clinical trial design.

Panel discussion
Following the presentation, the floor was opened for comments and questions. The following points were raised by audience members for consideration:

- Dr. Strati: CD16 is crucial for both anti-dependent and direct cytotoxicity mediated by NK cells, but it is naturally cleaved by ADAM17 (ADAM Metallopeptidase Domain 17) and the half-life is short. Do you plan to control for this variable? Is fludarabine and cyclophosphamide still appropriate or is there an alternative regimen to use in this setting?

  o Dr. Fehniger: Regarding CD16, there are data showing CD16 is cleaved from the surface, though that may occur to avoid over-activating an NK cell. If CD16 is cleaved from the surface, there is restoration after a day or

Building on Recent/Novel Proof of Concept Treatments Summary (Session IV):

- Carefully designed clinical trials are needed to identify the optimal dosage and scheduling, especially in the time of COVID-19.

- Prospective integrated safety databases are needed to identify toxicity signals early in drug development.

- Retreatment approach vs indefinite treatment needs to be considered in clinical trial design.

- A better understanding of the TME and how therapies affect the TME is critical to understanding treatment sequencing, which remains a critical gap.

two once the cell is out of that environment. We are not engineering in any changes to CD16. If you are using allogeneic donors, you could can screen donors for polymorphisms. It is a challenge to control for the lympho-depleting chemotherapy that is necessary to have sufficient expansion and space for these cells to act. If this is conducted in the allogeneic setting, it is absolutely critical to suppress the immune system; otherwise, the cells are rapidly rejected. It does complicate the interpretation, and you would expect that this regimen has some activity in FL (eg, ZUMA-5 study). There are ways to design the trial endpoints to target a higher complete response (CR) rate. Another exciting area in the field is discovering ways to avoid T-cell recognition of cell therapy product, perhaps by homeostatic cytokines to expand the niche rather than having to use fludarabine and cyclophosphamide.

- Loretta Nastoupil, MD (The University of Texas MD Anderson Cancer Center): How can we enhance persistence of these products (eg, dosing multiple times or adding additional therapy such as CD20 antibodies) and how critical is it?

  o Dr. Fehniger: If you make them invisible, then you can enhance persistence. One of the main questions is what is the required time of opportunity (ie, a few weeks, months, years)? I would extrapolate from early data from CAR-T cells that if you treat a large cell lymphoma with CAR-T cell, they disappear after just a few months, yet patients do not have relapses. You probably need them to last for a few months, perhaps via repeated dosing of allogeneic cells. We will get more data from early phase clinical trials in the coming year.

- How much is known about what governs tissue homing and tissue infiltration of NK cells derived in this way?

  o Dr. Fehniger: We know that these memory-like NK cells will traffic to the bone marrow and they express L-selectin and other homing molecules required to get into lymph nodes. In order to better understand this, we will need biopsies in addition to blood analyses.

- Ahmet Dogan, MD, PhD (Memorial Sloan Kettering Cancer Center): Do you expect that the FLs with high NK cell content may have more mechanisms for trafficking? Can you select patients based on a 1:10 or 1:100 ratio of NK to B-cells that could give information about natural trafficking?

  o Dr. Fehniger: In normal lymph nodes, NK cells comprise about 1% of cells whereas in FL nodes, it varies from 0.5% to 10%. A lymph node does not need to be full of NK cells to get an effect since only a few antigen-specific T-cells are effectively performing that job. Also, there is the potential that if NK cells traffic to the lymph node, there will be recruitment of additional factors that may alter the TME and affect T-cells.

    ■ Dr. Dogan: If you give low-dose regular therapy, would you increase chance of NK cells trafficking?

- Dr. Fehniger: I have not seen specific evidence for that, but could be intriguing to explore.

Next, Gilles Salles, MD, (Memorial Sloan Kettering Cancer Center; Moderator), continued the discussion of emerging treatment strategies, by highlighting the shift from chemotherapy to immunotherapy.[Morschhauser, 2018; Morschhauser, 2021] Because the R2 regimen of lenalidomide plus rituximab was approved in the relapsed/refractory (R/R) setting,[Leonard, 2019] it could constitute a backbone in combination with other agents, such as tazemetostat, bispecific antibodies and others, which are currently undergoing clinical trials.[ClinicalTrials.gov, 2021; ClinicalTrials.gov, 2020] There are at least six CD3xCD20 bispecific antibodies under development with differences in the CD20 and CD3 domains, including epcoritamab,[Engelberts, 2020] glofitamab,[Bacac, 2018; Bacac, 2016] mosunetu-zumab,[Ferl, 2018; Sun, 2015] odronextamab,[Smith, 2015] plamotamab,[Patel, 2021] and IGM-2323.[Baliga, 2019] The importance of designing future trials to include step-up dosing to avoid cytokine release syndrome was demonstrated from the pivotal phase 2 clinical trial with mosunetuzumab monotherapy. In R/R patients, the ORR was 80%, with a CR rate of 60% and time to response of 1.1 months.[Budde, 2021] Additionally, the PFS was 17.9 months.[Budde, et al., 2021] In the R/R setting, glofitamab monotherapy was found to have an ORR of 81%, complete molecular remission (CMR) of 70%.[Dickinson, 2021] Glofitamab in combination with obinutuzumab had an ORR of 100% and CMR of 74%.[Morschhauser, 2021] Treatment with odronextamab (≥5 mg) in 32 patients with R/R FL achieved an ORR of 93%, CR

rate of 72%, and time to response of 1.1 months. [Bannerji, 2022] Overall, the CR rates among mosunetuzumab, odronextamab, glofitamab, and epcoritamab ranges from 50% to 72%. Based on these initial findings, it is likely that some of these agents will probably be approved in third-line or later settings for patients with FL. Many of them have been designed and investigated for use in combination with standard of care (SoC) and cytotoxic chemotherapy, which is a bit of a paradox, though the clinical results seem promising. Other combinations are emerging in early phase trials, such as those with anti-CD28 antibodies and tazemetostat. Taken together, this is a new field and an emerging new SoC. Some of the anticipated challenges include managing first infusion AEs (eg, step-up dosing), DOR, moving these agents into earlier settings (eg, designing optimal trials and selecting high-risk patients), teasing out the optimal combinations, and understanding the mechanisms of action (eg, antigen loss vs T-cell exhaustion, etc).

Loretta Nastoupil, MD, (Moderator), furthered the discussion by reviewing the ZUMA-5 study, which is underway to evaluate axicabtagene ciloleucel (axi-cel) in patients with R/R FL.[Neelapu, 2021] Despite FDA approval, axi-cel is underutilized in lymphoma because of issues related to logistics, cost, and access. Patients enrolled in ZUMA-5 were over-enriched for young, fit patients who could tolerate the toxicities as well as for poor-risk R/R patients. The PFS was more favorable in the FL cohort with POD24 (39.6 months) compared with the marginal zone lymphoma cohort (17.3 months), emphasizing disease-specific features that drive outcomes.[Neelapu, et al., 2021] A subgroup analysis of patients with R/R FL in the ELARA study were treated with tisagenlecleucel (tisa-cel), and notably, over half of patients received bridging therapy.[Thieblemont, 2021] The toxicity profile was favorable, with no grade 3 or higher CRS and only 1 patient who experienced a grade 3 or higher neurotoxicity.[Thieblemont, et al., 2021] Eighteen percent of these patients were managed in the outpatient setting, potentially reducing healthcare cost utilization.[Thieblemont, et al., 2021] Novartis has a novel turbo-charged CAR T-cell altered to be more memory-like with less exhaustion likely due to shorter manufacturing time, but also due to the lower quantity of cells infused. There will be a longer time to CRS, which is an important consideration for use in the outpatient setting. Although it is a one-time therapy, CAR T-cell therapy can lead to cell depletion for years and this needs to be taken into consideration. Advantages for using CAR NK cells over CAR T-cells include potential lower cost, outpatient administration in community settings, low or absent of graft-versus-host-disease, and favorable toxicity profile that lends itself to combination regimens. Therapy with a core blood-derived, anti-CD19 CAR NK cell is being assessed in patients with R/R B-cell lymphoid malignancies.[Liu, 2020] Another CAR NK cell, FT596, is being investigated in a phase 1 trial in patients with R/R B-cell lymphomas.[Bachanova, 2021] This therapy incorporates IL-15 receptor fusion and non-cleavable CD16 to enhance some of the limitations and has a very favorable safety profile, suggesting broader access. Another potential target is CD47+/SIRP+ macrophages, which is increased in patients with FL who relapse after R2 treatment. [Marques-Piubelli, 2022] Overall, there are a number of strategies beyond targeting a specific enzyme or pathway, and using cellular therapy might be one way to address the issues with the TME.

Panel discussion
Following the presentation, the floor was opened for comments and questions. The following points were raised by audience members for consideration:

- Do you think CAR T could be curative for FL, considering FL is very sensitive to T-cell-mediated graft vs tumor effect?

  o Dr. Nastoupil: Yes, I think CAR T could be a curative component of FL. Currently, we see a higher percentage of patients without a progression event but not clear stabilization.

  o Dr. Salles: The relapse of the disease originates from the CPC population. Are we able to destroy this population, or are we just controlling it? Regarding allogeneic transplant, patients keep their T-cells active, so I think the question of persistence is relevant and may be crucial for FL.

- If bispecific antibodies get approved in the R/R setting, how do you decide between bispecific antibodies vs CAR T in an academic center that has access vs a referring physician who needs to be educated at a distance? Should the physician administer bispecific antibodies locally and then refer for CAR T therapy?

  o Dr. Nastoupil: I anticipate most patients will have a bispecific antibody before they receive CAR T, though the challenge is predicting the toxicity (eg, CRS). Though I do think they will have better uptake, we need to do a better job of defining those patients who will have grade 2 or higher CRS, which I think are the same patients who experience toxicities with CAR T (ie, high tumor burden, circulating B-cells, high LDH). A major unmet need is a strategy to de-bulk these patients before they go onto bispecific antibodies, at least those who will be at high-risk. We underutilize our radiation oncology colleagues, as Dr. Pinnix has looked at 4 Gy as a potential strategy to de-bulk some of these patients before they go to CAR T.

- In terms of tFL from CAR T or bispecific antibodies, could you help us tease out what we have learned from clinical trials and real-world experiences regarding response rates and durability? What do we know about outcomes in tFL?

  o Dr. Nastoupil: In generally, outcomes in tFL are more favorable, but an unmet need is more large, real-world datasets. We also need to do a better job characterizing relapses in tFL.

- Do you think that the 24-hour turnaround time for the new CAR T product will improve results or make them worse?

  o Dr. Nastoupil: In general, I do not think we need a shorter turnaround time for FL, but it will provide an advantage for a more favorable phenotype for that specific CAR T cell, resulting in better outcomes. Time from enrollment to cell infusion was prolonged, particularly in the BELINDA and JULIET studies, which led to less favorable outcomes.

- Is the role of CD19-targeting agents in FL as a single agent and/or in combination similar to CD20-targeting ones?

  o Dr. Salles: Monotherapy with Fasinumab *(REGN475)* has 20% to 30% response rate and less than a 10% CR rate. In select patients, the BELINDA study had good results. Previous trials of CD19 agents were halted due to neurotoxicities, but raised the question of, are we observing something unique with CD19-directed therapies when we activate T-cells vs CD20?

    ■ Some companies are moving forward with CD19 agents in FL, which is not the most optimistic approach.

- Ryan Lynch, MD (University of Washington): The FDA has a very fixed mindset about what patients should receive in the frontline setting, and we had to put very specific language in our informed consent form regarding agents of known clinical benefit. How do we move beyond chemoimmunotherapy in the frontline setting given the regulatory challenges and considering other agents that work well?

  o Dr. Salles: How do we design studies to change SoC? I think we should make strides to get some of these agents with a high chance of success in the frontline setting. We will probably face similar challenges with the FDA. We need to understand how these drugs work or do not work in treatment-naïve patients.

- Dr. Ansell: Regarding moving toward a potential cure in FL and immunotherapy, it is critical to target B-cells because they define their environment. Secondly, T-cells replenish themselves in a heartbeat, but we are worried about therapies that destroy them. Perhaps it could be a good thing to destroy them and have fresh T-cells. If we are curing some FL patients, why are we not taking a potentially curative therapy to the frontline? Should we not put our efforts into accomplishing this?

  o Dr. Nastoupil: I agree, though the challenge is how to define a high-risk patient that people will accept the potential toxicity and convince the FDA that its justifiable. First, you will need single-arm single center phase

1/2 studies, followed by small, multicenter study, and if you see a signal without toxicity, then you will need to randomize to chemoimmunotherapy. Once efficacy is demonstrated in high-risk patients, then it can potentially be opened up to lower-risk patients.

- Dr. Ansell: Is there a merit to consider young people? If you are a young patient (35 to 40 years old) with FL, you may be in trouble when you are 60 years old. Would younger patients be more willing to take on that risk?

  o Dr. Salles: We are missing some information (eg, MRD) as well as how to prevent and manage toxicities, particularly in bispecific antibodies.

- I would like to push against idea that we have any confidence that CAR T cells cure FL patients today. We are hopeful of that but follow-up requires at least a couple of years. The idea to conduct a study in young patients is another thing. I think we do cure some patients with chlorambucil, R-CHOP, BR, CAR T, and other agents. There will always be some patients who meet a definition of cure if they die without a relapse. However, I think we need another decade to say that CAR T cell therapy is better than other therapies.

- Regarding giving young patients giving CAR T therapy, we need to first make sure it is very safe across a large group of patients before moving it upfront.

  o Dr. Nastoupil: In general, we are optimistic with the observed CAR T efficacy but are not naïve to moving it to frontline. The next step is to randomize trials, which are launching now. Bispecific antibodies lend themselves well to combinations, which is one limitation of CAR T in FL. We need to better understand why CAR T cells work in FL.

  o Dr. Salles: Whether they are bispecific antibodies or engineered CAR T cells, biological agents hold promise. Drug development for CAR T cells has huge obstacles, including production limits and a highly competitive field. However, the biology we learn in this field will help us to develop safer and more efficient products. The situation is similar for bispecific antibodies, where drug modifications are evolving and need to be clinically tested. Overall, they hold substantial promise for patients, especially until we have a broad epigenetic target to change the fate of these cells.

- Dr. Lossos: FL is still an indolent disease and patients are surviving 15 years or longer, with some patients requiring intermittent therapies; thus, the QoL of patients need to be considered. Why not use CAR T cell therapy in indolent disease? And if so, patients need to be selected for carefully and prepared for differently.

  o Dr. Salles: This is a good point that comes back to the discussion about QoL, including side effect management. We need to identify the patients who might experience severe side effects and find ways to balance chronic and acute toxicities. We should not say we are going to cure patients with CAR T cell therapy, but we should mention that because it is a systemic agent, it is not toxic-free.

- Most of us use BR in the frontline setting, which revealed fatal toxicities in clinical trials; however, treatment-related mortality for CAR T cells is less. Despite a slightly different patient population, we cannot hold CAR T to different standards compared with other therapies.

- Lee Greenberger, MD (Leukemia & Lymphoma Society): CAR T is a living drug that may be there 10 years or more; therefore, is a bispecific antibody better than a CAR T-cell? For patients who could be potentially cured, do we need to consider turning off the CAR T-cell?

  o Dr. Salles: We do not need to kill CAR T-cells that are dormant, but it is difficult to extrapolate for the persisting ones. The proportion of patients that have somatic Ig hypermutation is about 30%. We have seen these patient populations in other trials. I have stopped rituximab maintenance during the COVID-19 pandemic, which makes extrapolations difficult. There is a trade-off between the toxicity of maintenance and coming back to the hospital with the risk of COVID-19. How we will continue to handle this situation in the future is still uncertain. Ideally, I would like to do some re-call of T-cells every 2 months with the rituximab, though this is not the preferred time during the pandemic.

■ Dr. Greenberger: If your B-cells are suppressed, you are probably not going to respond well to the COVID-19 vaccines.

o Dr. Nastoupil: We do not know how to dose the bispecific antibodies as the studies are all designed differently, and some patients continue until progression or intolerance, which is not an effective strategy in FL. Continuous therapy is going to result in long-term B-cell depletion. We to better understand what is driving severe persistent cytopenias that prolongs the risk for infection. In the myeloma community, some patients are getting boosted with stem cells, which is not a viable option in FL.

Emerging Treatment Strategies Summary (Session V):

·   There is a need for development of novel agents, including modified NK cells and CAR-T cells as well as novel strategies, such as using R2 as a backbone for different combination therapies with bispecific antibodies.

·   As novel agents and strategies emerge, gaps exist for identifying optimal candidates (low-risk vs high-risk patients) and how to minimize toxicities. Factors such as logistics, cost, and access need to be considered when creating new agents.

·   Well-designed RCTs requires the expertise of the LRF and its members, and they are critical for bringing novel therapies to market.

·   Rather than improving outcomes in later lines, we should consider shifting the focus to frontline therapy to provide an earlier cure, which would require a better understanding of how different therapies work in treatment-naïve patients as well as defining high-risk patients.

·   There is a need for collaboration with radiation oncologist colleagues to de-bulk patients, specifically with regard to patients who may receive bispecific antibodies and/or CAR T cell therapy.

·   Some controversy surrounds selecting therapy with CAR T cell vs bispecific antibodies, with regard to providing a cure and associated toxicities.

Session VI: Future Research Priorities and Opportunities – *John Timmerman, MD, UCLA Oncology Center (Speaker)*

To conclude the workshop, Dr. Timmerman presented six future research priorities and opportunities for the LRF, including (1) identifying a prognostic tool to accurately predict risk factors;[Casulo, 2021] (2) optimizing initial treatment algorithms according to risk, age, and fitness; (3) devising the optimal way and frequency to monitor disease; (4) determining the optimal sequencing of therapies; (5) developing viable models of FL; and (6) preventing and treating transformation. Knowledge of patient and tumor-specific factors associated with risk of disease progression, transformation, and premature death from FL may permit us to select less-intensive vs more intensive initial therapies, and importantly, tailor therapies to molecular or immunologic features. However, several of the initial therapies are still being used and therapies are not being tailored to the molecular phenotype because this is not yet achievable. While there are a number of clinical tools at diagnosis as well as tumor biology and genetic tools, they require further refinement. There are some single genes that are associated with better outcomes, such as EZH2,[Huet, 2017] that information is not necessarily used to guide initial therapy. NGS panels (even limited ones) should be integrated into early treatment decision-making. NCCN guidelines lists agents in alphabetical order, suggesting no preference for treatment sequence, further underscoring that treatment is not tailored to disease and patient characteristics.[NCCN, 2022] Dr. Timmerman emphasized the need for more rational choices of initial therapy to preserve optimal performance of subsequent therapies, particularly immunotherapies and in the transformation setting. Chemotherapy-free regimens should be introduced for nearly all patients, reserving it only for those unresponsive to immunotherapy. Regarding disease monitoring, using ctDNA and CAPP-Seq would be ideal for gaining biologic information to adapt therapy. According to NCCN guidelines for surveillance imaging, a patient could be exposed to over 25 CT scans during their lifetime, putting them at unnecessary risk.[NCCN, 2022] At diagnosis, MRI scans should be used, especially for younger patients, and CT scans should be reserved mostly for patients enrolled in clinical trials. Data show that only 14% of relapses are identified by CT scan in the absence of symptoms.[Rutherford, 2019]

The current method for determining sequencing of therapies does not address the ongoing evolution with increasing genomic complexity and danger. Progressing mutations requiring treatment are not necessarily the same as those that occur at transformation and could account for why some patients never transform.[Kridel, 2016] Can earlier, more aggressive interventions to target FL-specific pathways halt further evolution and transformation? Therapy should be adapted to the molecular and immunologic features of each FL case using NGS, epigenetic profiling, and/or immune and TME assessments. Based on that data, tumor could be disarmed via agents such as EZH2 inhibitors, IMID, HDAC3 inhibitors, and checkpoint blockades. Finally, the tumor could be destroyed using mAbs, CAR T cells, bispecific antibodies, NK cells, and perhaps chemotherapy. Progress in FL research has been slowed by the inability to culture tumor cells in vitro or establish cell lines in immunodeficient mice in vivo. The development of FL models, however, would permit the screening of novel therapies and combinations, as well as examining mechanisms of resistance. Excitingly, a new xenograft model of human FL has been generated by Dr. Louissaint, and several syngeneic immunocompetent murine models of FL are being created by Dr. Melnick. Transformation is heterogenous and not typically predictable; thus, it should be a priority to create improved in vitro and in vivo models as well as cell lines derived from patients with tFL treated with modern therapies. Importantly, there is a need for a repository of annotated tFL cell lines and PDX models pre- and post-treatments that is shared amongst investigators. Another way to prevent transformation is to eliminate (or cure) FL clones early before transformation occurs. A long-term follow-up study of the SWOG-0016 trial found that the OS and PFS curves flatten,[Shadman, 2018] suggesting that some of these patients are cured and perhaps we will see more of this pattern in future studies.

Panel discussion

Following the presentation, the floor was opened for comments and questions. The following points were raised by audience members for consideration:

- Dr. Yahalom: One to about 5 patients with FL present with localized disease and we hardly addressed the issues that these patients bring. Eventually, some will relapse in more distant areas and this population may have different sub-groups. Some of these patients are curable, and while we discuss the best treatment strategy, we still lack prospective studies that examines no treatment, rituximab, chemotherapy, combination, radiation, QoL, and cost. It is interesting to observe how some patients respond to different radiation doses and affects risk for transformation. Importantly, future meetings should include radiation oncologists to break the barriers between treatment modalities.

    o Dr. Timmerman: It would have been great to discuss some of the data regarding in situ vaccination and combining radiation therapy with various agents.[Hammerich, 2019] We should be thinking more about these types of strategies, as there is a large role for radiation, and have more multicenter approaches for conducting these types of studies.

- Mitchell Smith, MD, PhD (Follicular Lymphoma Foundation): I would be cautious about localized FL, in that it might be different biology. A key question is, how will we get to the point of knowing what is best?

    o Dr. Timmerman: How long of a PFS would you want to see to be convinced that we have achieved a cure?

        ■ Dr. Smith: It takes years, and we need the tools to ask if we have eliminated the clone or some epigenetic marker. We need that assay because otherwise, we are not sure and patients really want to know.

- Dr. Timmerman: A patient on the ZUMA-5 trial was treated and gone into complete remission and 5 years later, the transformed clone could not be found, demonstrating at least a partial victory.

    o Dr. Smith: We need to examine those individual clones on the molecular level as best as possible to advance the field faster.

- Dr. Evens: We should consider the concept of the functional cure where a patient has an expected lifespan despite diagnosis. However, in order to define cure, we need technologies sensitive enough to detect residual DNA, and I am not sure that we have these tools yet. ctDNA/ CAPP-Seq does not have sufficient sensitivity. We want to be able to interpret the negative tests, but we do not know how to accomplish that yet.

    o Dr. Timmerman: I think there is a role for ctDNA in FL; for example, a POD24 patient in metabolic CR and MRD positive should have consolidative therapy to eradicate the clone, though we need to be able to detect it.

        ■ Cure depends on the patient population and treatment goals. For example, goals may differ between a 75-year-old person with comorbidities compared with a patient who is 40 to 50 years old with no comorbidities. Cure may be easier to accomplish in high-risk patients since they relapse early, but that cannot be done in low-risk patients who relapse 15 years later.

    o Dr. Timmerman: Regarding younger patients under the age of 40 years, the chance for progression is very high unless we continue to make strides in curing the disease. The younger they are, the more concerned we are about applying aggressive treatments.

        ■ The younger patients will be important for determining if a cure can be achieved since we can follow them for a longer time.

- What if we observe that CAR T therapy cures 40% of patients, but the OS curve closes after 10 years? Can that be the primary endpoint of randomized phase 3 trials?

  o Dr. Timmerman: FDA will approve therapies using median PFS.

    ■ For PFS, you may see the lower treatment effect or R2 but you could potentially see an early tail of the curve.

  o Dr. Timmerman: An early plateau may indicate we have cured some patients. The minimum amount of time is probably about 5 years for PFS curves to mature. The update of the ZUMA1 study has shown that the curve is leveling off now at 5 years of follow-up time.[Jacobson, 2021] It would be encouraging to see a similar curve in the ZUMA5 trial.

- Dr. Cheson: The question that needs to be addressed is not PFS, but rather lymphoma-specific survival and this needs further discussion.

  o Dr. Timmerman: Lymphoma-specific survival is important, though we also have to examine OS.

  o Dr. Lossos: It is not enough to collect only PFS, but also beneficial to collect lymphoma-specific survival data.

  o At the FDA meeting regarding PI3K inhibitors, they made it very clear that for therapies with modest toxicities, they want companies and investigators to consider OS, not only as a measure of survival but as a measure of toxicity.

- Dr. Timmerman: We need to be pushing development of more aggressive yet safer therapies.

- Dr. Lynch: How is "cure" defined in other cancers?

  o Dr. Timmerman: Cure is not often defined in other cancers, though in the immunotherapy field and melanoma patients, they observe that PFS follows very closely with OS. In contrast, PFS and OS are uncoupled in FL because of the longer natural history of disease. In metastatic breast cancer, they have the same issue and do not use the word "cure."

Future Research Priorities and Opportunities Summary (Session VI):

- Clinical tools, including prognostic ones, need further refinement in order to align the molecular phenotype of the tumor with treatment and to know if a cure has been achieved.

- Improved cell lines and animal models are needed to screen novel therapies and mechanisms of resistance as well as repositories of annotated cell lines and models of pre- and post-treatment shared by investigators.

- There is a need for prospective studies examining no treatment, rituximab, chemotherapy, combination, radiation, QoL, and cost.

- Further discussion is needed surrounding the definition of "cure" and the optimal clinical trial endpoints (ie, PFS vs OS vs lymphoma-specific survival).

Summary

The inaugural 2022 International Follicular Lymphoma Lymphoma Scientific Workshop covered the latest research in various areas that have been identified as contributors to the unmet needs and gaps in FL, along with providing a platform for lymphoma experts to discuss the latest treatments and optimal strategies for improving patient care and clinical trial design. The generous support of the Jaime Peykoff Family has made possible the funding of ten investigator grants, five of which were spotlighted in this report, and are accelerating critical research. Continuing efforts are needed to better understand the underlying biology of this heterogenous disease and to devise sensitive clinical tools and models. In the future, the results of current and new studies will be used to advance drug development, inform treatment selection, and improve both survival and QoL outcomes for patients that the LRF serves.

Acknowledgements

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