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Lymphoma Research Foundation Follicular Lymphoma Discovery Meeting:

A LYMPHOMA RESEARCH FOUNDATION WHITE PAPER

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Table of Contents

2 Introduction

3 Summary of the June 30th Discovery Meeting

3 Disease Biology and Prognostic Factors (Session I)

5 Risk Factors (Session II)

7 Transformed Disease (Session III)

9 Current and Emerging Treatment Strategies (Session IV)

12 Discussion and Roadmap Creation (Session V)

13 Research Priorities Roadmap

14 Agenda

Introduction

On June 30, 2020 the Lymphoma Research Foundation (LRF) convened a group of the world's experts on follicular lymphoma (FL) via a day-long online program to discuss the inception of the new Jamie Peykoff Follicular Lymphoma Research Initiative. As described by Andrew Zelenetz, MD, PhD, (Memorial Sloan Kettering Cancer Center), Chair of the LRF Scientific Advisory Board, the initiative will provide support for both early career and senior investigators pursuing clinical and translational research. Dr. Zelenetz highlighted several areas of interest, including the fact that despite improved outcomes for follicular lymphoma in the rituximab era, the predominant cause of death in FL patients remains lymphoma. Many of these deaths are related to transformed disease, which carries a significantly worse outcome and for which scientists are still striving to understand the clonal-sequential process of transformation from indolent to aggressive disease. Despite ongoing efforts, there remain few treatments that can offer a cure for follicular lymphoma.

The purpose of this meeting was intended to guide the development of a research program that will focus on areas of greatest unmet need and to create a roadmap for the future of follicular lymphoma research moving forward.

Following the workshop, the Follicular Lymphoma Initiative Steering Committee drew on the discussion of the June 30 meeting to create a roadmap of research priorities for follicular lymphoma. Future efforts of the Initiative will draw on this roadmap to develop both funding mechanisms for follicular lymphoma research as well as additional scientific workshops in these areas.

Summary of the June 30th Discovery Meeting

Session I: Disease Biology and Prognostic Factors

Session I provided an overview of the biology of follicular lymphoma and prognostication. The first presentation from Laura Pasqualucci, PhD (Columbia University) highlighted that, despite unmet clinical needs for patients with progression of disease within 24 months from first treatment (POD24) and/or with transformed disease (tFL), who have significantly worse clinical outcomes, we do not yet have a strong biological understanding of what distinguishes patients at higher risk of early treatment failure. Further knowledge about the complex pathogenesis underlying these processes before the final clonal expansion of B-cells in the germinal centers (GC) is key.

The critical t(14;18) translocation is acquired in pre-B cells but is not sufficient for malignant transformation, as peripheral blood cells carrying this translocation can be found in as many as 70% of healthy subjects, yet most of these individuals never develop follicular lymphoma. Additional genetic events facilitated by errors during somatic hypermutation and class switch recombination, along with iterative cycles of GC re-entry and re-initiation of secondary GC responses are required for malignant transformation. In addition to BCL2, mutations in chromatin modifiers such as KMT2D, CREBBP, and EZH2 appear to represent early events acquired by a common FL precursor (as was discussed extensively later in the meeting in session III). Mutations common in the dominant tFL clone affect regulators of the cell cycle, DNA damage response, and proliferation including MYC and TP53, as well as genes involved in immune evasion like B2M. However, robust genetic predictors of transformation are still lacking.

Per Dr. Pasqualucci, open questions remain concerning how FL develops including the precise hierarchy of genetic events that lead to the emergence of dominant clones in FL, whether we can identify and target the FL common precursor, whether we can recognize patients at higher risk of developing FL, , and how best to understand the genetic heterogeneity of FL.

The next presentation from John Timmerman, MD (University of California. Los Angeles) discussed the immunology and intratumoral microenvironment of FL. One of the unique features of FL is dynamic immune surveillance with a waxing and waning clinical course and a higher spontaneous regression rate of any cancer, with up to 25% of patients having some degree of spontaneous regression. The mechanism for this is thought to be mediated by active tumor killing by cytotoxic T-cells. However, intratumoral Treg cells have been shown to express CTLA-4 which suppress cytokine production by effector T-cells that themselves express PD-1. There appear to be two separate PD-1+ T-cell populations in FL: interfollicular T-cells, TIM-3+ with an exhausted phenotype and PD-1-dim and another within follicles of the T-follicular helper cells (Tfh). The interplay between the infiltrating host immune cells and the tumor cells including Tfh, dendritic cells, and macrophages appear to promote the growth of FL.

The expression of PD-1, CTLA-4, and TIGIT on the host immune cells provide the rationale for the clinical manipulation of the tumor microenvironment. Some examples include the use of idiotype-pulsed dendritic cell vaccination and the use of TLR9 agonism to activate the immune response following radiation of a single site, leading to an abscopal effect with tumor shrinkage at untreated sites in the majority of patients.

According to Dr. Timmerman, the immunobiology of the tumor microenvironment and the interplay between FL and T-cells, macrophages, and APCs including immune checkpoints is an area ripe for study. Open avenues for research include the nature of the endogenous immune response to FL including whether there are unique epitopes to each patient or common shared antigens, as well as exploring the pathways that limit the effectiveness of the host response in suppressing FL. "The first time we say 'cure' in follicular lymphoma is likely to involve some form of immunotherapy," he said.

Stephen Ansell, MD, PhD (Mayo Clinic, Rochester) next discussed the prognostic and predictive factors in FL, noting as described earlier that lymphoma remains the leading cause of death for patients with FL, typically due to transformed or resistant disease. He identified POD24 as perhaps the best prognosticator for outcome, but noted the limitation that it is essentially a clinical measure that cannot make any predictions up front. The GELF criteria and Follicular Lymphoma

International Prognostic Index (FLIPI) give some prognostic clinical information, but do not provide us any informative data that changes major clinical management or treatment decisions.

Other studies have attempted to incorporate genetics, B2 microglobulin, or levels of infiltrating immune cells into prognostic scoring systems, but many of these models have yet to be clinically reproducible. Currently, POD24 remains the most consistent predictor of a poor outcome in FL, but this severely inhibits the ability to alter treatments up front. Additional understanding of genetics and biology as predictors for early progression and transformation is a crucial area of research for FL moving forward.

Session I Discussion

Following the presentations in Session I, Dr. Zelenetz proposed the following question: "What do you see as the single most critical piece of information that needs to be answered about FL biology and prognostication?"

The following questions were proposed:

- Justin Kline, MD (University of Chicago): How can we best understand the genetics and/or tumor immune features that lead to early progression after therapy? Can we develop therapeutic targets for these patients rather than empiric approaches?
- Brian Link, MD (University of Iowa): Why does FL recur after seemingly deep remissions? Does recurrent FL derive from resistant clonal cells or new offshoots from progenitor cells?
- Dr. Zelenetz and Andy Evens, DO, MSc, FACP (Rutgers Cancer Institute of New Jersey) raised similar questions: What is it about the tumor cell that invokes the microenvironment's response? Why does it seems to sometimes be dependent on the microenvironment, but independent of the microenvironment at other times?
- Ash Alizadeh, MD, PhD (Stanford University): Using paired FL progressions with and without transformed disease with associated tumor and blood specimens, can a faithful model of transformed FL that can be manipulated be developed?
- Connie Batlevi, MD, PhD (Memorial Sloan Kettering Cancer Center): Can a large scale biology-of-disease project be built following both tumor and TME? Factoring just genetics and just TME does not appear to be enough.
- Jessica Okosun, MD, PhD (Barts Cancer Institute, QMUL): We need a better understanding of the different molecular phenotypes that drive different clinical behavior including POD24, transformed disease, and watch-and-wait.
- Drs. Ash Alizadeh, Sonali Smith, MD (University of Chicago), Andy Evens, Connie Batlevi, and Laurie Sehn, MD, MPH (BC Cancer) discussed the feasibility of combining samples from large cooperative group studies.

Session II: Risk Factors

Session II focused on risk factors for FL, including the genetic and environmental aspects of risk pre-diagnosis, as well as long-term risks for FL patients including second cancers and associated malignancies.

James Cerhan, MD (Mayo Clinic, Rochester) presented the first section of the session discussing the epidemiology and genetic risk factors of FL. FL represents 12% of mature non-Hodgkin lymphoma (NHL) in the US with the highest incidence in whites and significantly lower incidence in black patients, suggesting that inherited predisposition may play a role. Interestingly, data show that Asian patients born in the US had increased rates of incidence relative to those born outside the US and that migration from Hong Kong to British Columbia increased rates of incidence, suggesting a role for environmental factors as well.

Family history of hematologic malignancy is associated with an 80% increased risk of lymphoma overall, but the highest risk is for a family history of the same lymphoma subtype. For patients with a family history of any hematologic malignancy or NHL, their risk for FL did not vary versus other lymphoma subtypes even after adjusting for environmental factors. No major genetic loci have been identified in linkage studies in families, pointing instead to common variant alleles with small effect size distributed over multiple genes.

The NHL genome-wide association study (GWAS) study identified the strongest locus of association with follicular lymphoma at 6p21 in the HLA region with five other susceptibility loci identified genome-wide (including one unsurprisingly associated with BCL2). These loci are common with allele frequencies greater than 5%, have small effect sizes and have largely unknown function. Further insights into the genetic architecture of FL risk are needed including the identification of additional SNPs, rare variants, and population specific effects. Other areas of interest for further research are the integration of tumor and host genetics, genetics of precursor conditions, and the development of polygenic risk scores, as well as genetic interactions with the environment.

The second presentation, presented by Christopher Flowers, MD, MS (MD Anderson Cancer Center), detailed the data for clinical, lifestyle, and environmental factors associated with developing FL. Several factors from patients' clinical and medical history have previously been identified that appear to be protective against FL including allergy history and atopic disorders, while Sjogren's syndrome in women appears to be a strong risk factor for the development of FL. Occupational exposures including exposures to tobacco, benzene, toluene, and xylene as well as chlorinated hydrocarbons have also been identified as possible risk factors, with spray painters who are exposed to these chemicals found to be much more likely to develop it than their peers. Family history of lymphoma also appears to have an associated and there is a weak association between young adults with elevated BMI as well.

Dr. Flowers raised the question that having identified high risk groups such as women with Sjogren's syndrome, spray painters, patients with a strong family history of NHL, or high-risk genetics, could it be possible to screen these groups for high-risk lesions such as t(14;18) and a CREBBP mutation? Following from that, could we consider targeted low-toxicity therapy for these at-risk individuals with the goal of eliminating precursors and preventing the transition to overt lymphoma? Additional questions include whether we need additional data and what clinical trial infrastructure is needed, including the possibility of prevention clinics, to pursue these studies.

Lindsay Morton, PhD (National Cancer Institute) presented data on the long-term risks for patients with FL. While over the past several decades the incidence of FL has remained stable, mortality is decreasing. Management of the long-term risks of FL such as the risk of subsequent malignancies, immune abnormalities and treatment-related adverse outcomes have become increasingly important, as has understanding the impact of lifestyle and medical history on survival. Therapy-related AML or MDS are important complications of FL treatment with an approximately 8-fold risk, particularly in younger patients. They are also at slightly higher risk for solid malignancies such as lung cancer and melanoma as well as other types of lymphoma.

There are currently conflicting results from the literature regarding the impact of lifestyle factors such as obesity, smoking, and alcohol and little data regarding risk factors from patients' medical history. There is a suggestion of increased risk for smokers, but this

may be a question of lymphoma-specific survival versus overall survival. There is also a gap in the literature regarding long-term immune abnormalities and their consequences for patients with FL. Many barriers to answering these questions remain including issues with sample size, obtaining clinical data, and maintaining systematic long-term follow up.

Session II Discussion

Following the presentations in Session II, the following points of discussion were raised:

- John Leonard, MD (Weill Cornell Medicine): The long-term immune function of patients seem to be a manageable and important aspect of post-treatment survival that the LRF could be interested in. Immune function is both impacted by and impacts therapy.
- In response to Dr. Leonard above, Dr. Morton suggested using pre-diagnosis samples and then following serial samples over time. She also discussed leveraging other existing resources that already exist such as other large-scale genetic studies and analyzing that data to search for risk factors and analyze long-term outcomes.
- Dr. Chris Flowers agreed and suggested trying to combine the epidemiological side with epigenetic studies of tumor and microenvironment to attempt to better understand how they interact, particularly given our lack of knowledge of the variability of the effects of the tumor microenvironment.
- Dr. John Timmerman: Understanding post-treatment long-term immune function and fitness may be key to prolonging survival as it may affect outcomes to immunotherapies.
- Dr. Jim Cerhan concurred that ancillary studies of existing larger studies will be key to identifying risk factors moving forward.
- Dr. Sonali Smith: The impact of immune abnormalities appears to be affected by germline, somatic, and treatment effects. How can this best be studied? Dr. Morton responded: no data yet exists, but perhaps serial specimens from clinical trials over time can help answer this?

Session III: Transformed Disease

Dr. Brian Link began Session III with a brief overview of transformed follicular lymphoma. Although odern cohorts suggest that the risk of transformation may be only 2-3% per year, and may not be as catastrophic as once thought, particularly for those who transform l ater in the course of their disease and who are anthracycline naïve, , studying transformed disease remains an important area of need for the LRF given data suggesting that over half of lymphoma deaths from FL are from transformed disease., Data from a cohort from British Columbia patients who had POD24 events on modern bendamustine-rituximab therapy revealed that 76% of those events were transformed lymphoma suggesting that all strategies to control FL globally may not have the desired impact on transformation as a threat. Dr. Link proposed that "the best chance in improving outcomes lies in understanding what was brewing under the hood" before we recognized the presence of transformed disease.

Joseph Schroers-Martin, MD (Stanford University) presented on behalf of Dr. Ash Alizadeh about understanding the pathogenesis of transformed lymphoma. Data have shown that transformed FL arises more frequently by branched evolution from a shared mutated progenitor cell. Implications of this include subclonal heterogeneity as well as the co-existence of FL, transformed FL, and precursor cells in the germinal center and marrow and the early existence of chemo-resistant subclones. Data from the Alizadeh lab shows that BCL2 translocation positive blood samples are associated with significantly higher mutational burden than blood donor controls, even in patients that never go on to develop FL. Patients with transformed disease also have a higher non-concordant mutational burden than non-transformed relapsed FL, consistent with branched evolution. However, it is unclear whether this implies subclonal heterogeneity present early on or whether they come to prominence by selection. As discussed earlier, some acquired lesions are associated with transformation, such as those affecting cell cycle regulators, NF-kB associated genes, immune evasion and response to DNA damage; however, many of these are also associated with FL and there is no "smoking gun" associated with transformation. Acquired mutations may be early subclonal events, as evidenced by the fact that dominant mutations in transformed disease have been shown to be present in low allelic frequencies in pre-transformation biopsies.

Transformed FL seems to be associated with a stem cell-like signature, with enrichment of MYC and its targets. Shared truncal lesions seem to persist in transformation, such as those in CREBBP and KMT2D, as well as acquired N-glycosylation sites, and they remain stable from diagnosis through transformation and subsequent therapy.

Dr. Schroers-Martin presented unpublished data from the Alizadeh lab looking at BCL2 translocation positive pre-diagnostic blood samples from healthy individuals in the European EPIC cohort who eventually developed follicular lymphoma. He showed that CREBBP mutations were frequently detectable, even with a mean time to diagnosis of FL of 7.8 years. The relative allelic ratio of t(14;18) to CREBBP was higher in pre-diagnostic samples but approached comparable levels in mature FL tumors, suggesting that the BCL2 lesion preceded the CREBBP lesion and that this clone subsequently came to dominate. Analysis of mature FL cells, hematopoietic stem and progenitor cells (HSPCs), and non-B cell populations from patients with CREBBP mutations showed that the mutationwas present in tumor cells but not HSPCs or non-B-cells. Sequencing from paired FL and post-treatment lymph node biopsies also showed persistent low-level CREBBP in 2 patients prior to relapse. This data suggest that truncal CREBBP lesions appear localized to committed B-cell lineage and may persist after treatment in a population of common progenitor cells (CPCs).

One of the most important open questions in transformed FL is whether patients can be risk-stratified for their chances of transformation at diagnosis or after first-line treatment. Some data suggest that circulating tumor DNA may have a role in predicting which patients eventually transform. Another key in answering this question may lie in understanding the population of resistant cells that drive relapse post-transplant, and evaluating their characteristics so they can be identified at diagnosis or after initial therapy.

Session III Discussion:

- Dr. Schroers-Martin: Important benchmarks in this space remain, including the development of an operational definition of transformation including genetic, transcriptional, immunologic, and tumor microenvironment definitions. The question remains whether the detection of early transformation can be clinically useful if they can be detected, and whether we should attempt to treat the common precursor or the aggressive clone.
- Dr. Jessica Okosun: The genetics, epigenetics, and microenvironment all play a role and represent a multitude of layers, and understanding transformation requires understanding of their interplay
- Dr. Laura Pasqualucci raised the question of whether CREBBP can be definitively shown to be a later lesion than the t(14;18) translocation. Dr. Schroers-Martin brought up cases of t(14;18)-negative patients who bore CREBBP mutations but agreed that it appears to be a predominantly later lesion.
- Dr. Andrew Zelenetz noted that Dr. Alizadeh's data suggests that the CPC is a pre-B cell, while clinical and pathologic data support the idea that it's a mature B-cell. Dr. Alizadeh agreed that CREBBP mutants appear to be CPC lesions that are first detectable after B-cell lineage commitment but could not pinpoint exactly where in the B-cell lineage they occurred.
- Dr. John Timmerman asked how far away we are from screening high risk patients for transformation via blood, such as by ctDNA, and if detected early, what should we do about it?

Session IV: Current and Emerging Treatment Strategies

Dr. Sonali Smith introduced Session IV, the final session of the meeting, highlighting that despite many different clinical scenarios of FL including treatment naïve patients with high or low tumor burden, early progressors, relapsed and double-refractory FL, and despite the many treatment options available there remains no biologic basis on which to choose specific therapies. It is apparent that not all relapses are the same, with POD24 showing significantly worse outcomes and worsening PFS and OS with each subsequent relapse.

Ranjana Advani, MD (Stanford University) gave the first presentation describing the current landscape of approved therapeutic options for front-line disease. In the front-line treatment of follicular lymphoma, many effective treatments are available and not all patients require therapy. Currently, the only tool we have for selecting those that require therapy is the clinical GELF criteria, but within this group there are many options including chemo-immunotherapy with or without maintenance, as well as chemo free approaches. Given the multitude of options available, both goals of therapy and survivorship questions need to be considered when selecting a therapy.

For patients with low tumor burden, there is currently no evidence that early therapy improves overall survival, quality of life, or rates of transformation. For patients with high tumor burden, R-CHOP with or without rituximab maintenance and BR with or without maintenance are the main options, although neither the PRIMA or BRIGHT studies showed a difference in OS with maintenance rituximab. The GALLIUM study showed a 7% improvement in PFS with obinutuzumab over rituximab but no OS advantage. Comparing R-CHOP and BR, the StiL and BRIGHT studies showed an advantage in PFS but not OS for BR over R-CHOP, with the GALLIUM study showing no difference. Interestingly, the StiL study which included no maintenance rituximab showed BR>R-CHOP for PFS while GALLIUM in which all patients received maintenance BR and R-CHOP were equivalent, raising the possibility that maintenance rituximab improves PFS after R-CHOP but not after BR. Another study has shown an advantage for patients after BR limited only to patients who achieved a partial response to therapy.

The chemo-free lenalidomide-rituximab regimen (R2) with rituximab maintenance has been shown to have equivalent efficacy to R-chemotherapy, although the duration of therapy is longer and it has a different toxicity profile.

POD24 remains a concern, and recent data has shown risk factors for POD24 include poor performance status, elevated beta-2 microglobulin, and high risk FLIPI as well as male sex. Obinutuzumab-chemo in the GALLIUM trial showed slightly fewer POD24 events versus R-Chemo but again showed no OS difference.

Some important areas for further study in the frontline treatment of FL include new criteria to stratify treatment as currently only the GELF criteria can be used to choose therapy. The role of rituximab maintenance and of the utility obinutuzumab remain unclear. It is important moving forward to be able to accurately risk-stratify patients and tailor their therapy to improve their quality and duration of response. The development of predictive biomarkers will be an important effort, as well as defining the best endpoints for clinical trials as overall survival can be difficult to meet in FL. Given the multitude of therapies available, analyses on quality of life and duration of therapy as well as cost are extremely important as well.

Dr. Sonali Smith next discussed the landscape of options in relapsed/refractory follicular lymphoma. While not all patients need therapy for relapsed disease right away, there are currently many options for relapsed disease including chemotherapy-based and chemo-free approaches.

For patients with low tumor-burden localized relapse, excellent outcomes have been shown with low-dose RT and this strategy remains a good option that is well-tolerated in this group. However, most patients require systemic therapy. Bendamustine-based options including BR and bendamustine-obinutuzumab remain options for refractory disease even in rituximab-refractory patients, with median PFS of bendamustine-based regimens yielding median PFS of approximately 2 years.

Chemo-free approaches that have recently been approved include three PI3K inhibitors: idelalisib, copanlisib, and duvelisib which have all been tested in heavily pretreated, refractory populations including high percentages of double-refractory patients. While CR rates have been modest and toxicity remains a limitation for combination therapy, they remain a viable option for this very refractory population. Another

chemo-free approach in relapsed FL is lenalidomide-rituximab, as shown in the AUGMENT study which included a large percentage of POD24 patients but no patients who were refractory to rituximab, and had an excellent overall response rate and CR rate of 34%. The MAGNIFY trial included refractory patients and gave R2 for 12 months, then randomized to continued R2 versus R-maintenance alone. This study showed similar rates of response and slightly higher CR rates, including good responses in rituximab-refractory patients. This raises the question of whether outcomes could be improved further with obinutuzumab.

The newest approval for relapsed and refractory FL is the EZH2 inhibitor tazemetostat, which showed good responses particularly in patients with mutant EZH2 although patients with wild-type EZH2 still saw some efficacy as well including patients previously refractory to rituximab.

Finally, both auto- and allo-stem cell transplants remain an option for early relapsed FL, although very few patients receive this therapy in 2020.

In terms of new directions for relapsed/refractory FL moving forward, an important question remains whether types of relapse should be more strictly defined and applied in trials, including POD24, EFS12, and double-refractory patients. As with front-line treatment, risk-stratification remains clinically based and the incorporation of biologic factors is an important goal. Other open questions include how best to measure endpoints in clinical trials given the difficulty of showing OS differences in this population and whether sequencing of therapies makes a difference.

The final presentation, given by Dr. John Timmerman, focused on investigational therapies for FL. There are several targeted small molecule agents recently investigated for relapsed/refractory FL, including ibrutinib, umbralisib, Syk inhibitors, and venetoclax. While results for trials of ibrutinib and fostamatinib have been disappointing, umbralisib (another PI3K inhibitor) showed an ORR of 52% and cerdulatinib, a combined Syk/JAK inhibitor, showed good responses as well. Venetoclax, a BCL-2 inhibitor, has shown results as a single agent as well and is now a building block for many new combination trials in FL.

Polatuzumab vedotin, an antibody-drug conjugate targeting CD79b, has been combined with rituximab and showed an excellent overall response and complete response rate, albeit with no PFS data due to short-term follow up. However, grade 3-5 adverse events were reported in 50% of patients raising concerns about its safety.

Several checkpoint inhibitors have been studied, although the results are mixed. Single-agent nivolumab showed extremely poor response rates, while pembrolizumab combined with rituximab in rituximab-sensitive patients showed an impressive overall response rate of 80% with 60% achieving a complete response, although follow up is short. Ipilimumab, an anti-CTLA4 agent has shown neither activity as a single agent nor in combination with nivolumab. Other checkpoint targets include CD47, a macrophage target, which showed an overall response rate of 71% with a 43% CR rate in 7 FL patients. Other checkpoint targets currently in pre-clinical study include TIGIT, CD137/4-1BB, LAG3, and TIM-3.

Another new class of therapeutic agents are the bispecific antibodies mosunetuzumab and REGN1979. Mosunetuzumab showed overall response rates of 63% with a 43% complete response rate in an extremely heavily pretreated and refractory population with a high percentage of POD24 patients, while REGN1979 showed extremely impressive rates of overall and complete response of 95% and 77% respectively, although survival data is immature.

The use of CAR T cells has been an exciting development for the treatment of lymphoma and a few studies have shown promising results in FL. A study of 21 patients with heavily pretreated refractory or transformed FL who received CAR T cells with a 4-1BB vector against CD19 showed durable responses for the majority of FL patients who achieved a complete response, while the transformed patients had significantly more early relapses even after achieving a CR, although none were seen after 15 months. The ZUMA-5 trial which also included heavily pretreated patients with a high percentage of POD24 and refractory disease showed an impressive overall response rate of 95% with 81% achieving a complete response. However, median PFS was only 24 months without an obvious plateau which given the cost of CAR T therapy was disappointing. There are several other CAR T trials currently in progress.

Session IV Discussion

- Dr. Jessica Okosun: Given the growing therapeutic armamentarium in FL, should there be more of an appetite to leverage and maximise prior and ongoing trials to define predictive biomarkers of response and resistance, so we have better patient selection for existing treatments? Dr. Ash Alizadeh further asked the question that if such a biomarker is found, could de-escalation approaches be considered? Dr. Soni Smith further agreed with designing clinical trials stratified by risks.
- Dr. John Timmerman: Long-term immune fitness after many lines of therapy which can reduce patients' immune function may have important implications for considering the ordering of therapies. Dr. Soni Smith agreed with this point and further suggested that the role of the exhausted T-cell may play a critical role in understanding this.
- Dr. Ash Alizadeh raised the question of whether the biology of POD24 should be the focus instead of transformation, given that it is more objectively defined than transformation given the lack of uniformity for histological confirmation by biopsy. There was extensive discussion regarding the utility of distinguishing POD24 progressors from those with transformation and whether it is worthwhile to distinguish between the two. Dr. John Seymour, MD, PhD (Peter MacCallum Cancer Centre, Melbourne) brings up the importance of identifying a robust predictive index to identify the POD24 population in order to target therapies toward them. Dr Judith Trotman, FRACP (Concord Hospital, University of Sydney) suggests attempting to identify the characteristics of the subgroup of early progressors who do not die earlier, as currently we only have clinical measures. Dr. Alizadeh points out that we only have a "surrogate of a surrogate" currently. Dr Sonali Smith also raises the question of whether we should be routinely checking for POD24 in asymptomatic patients.
- Dr. John Leonard suggests a focus on a cure for FL rather than a focus on POD24, including how to cure it and how cure is defined. Many supported the idea of functional cure including patients who receive one treatment and never progress. Dr. Trotman further noted that patients pick up that we are focused on transformation and worry, and that instead we should emphasize that most do well. Dr. Justin Kline brought up that a key question here might be the difference between between DLBCL and FL that leads to cure in the former and relapse in the latter. Dr. Paolo Strati , MD (MD Anderson Cancer Center) further asked whether POD24 will even matter in the future given the number of patients now receiving R2.
- Dr. Ansell and Craig Portell, MD (University of Viriginia School of Medicine) described seeking determinants of several subgroups of patients: those diagnosed and never treated or treated once, occasional progressors, and early progressors. Biology of the first group important to addressing cure.
- Dr. John Seymour: TP53 mutated FL appears to have a distinctly different, and adverse, biology and could be chosen for specific treatment approach, although this accounts for only 4% of FL in the M7FLIPI dataset.
- Dr. John Timmerman: Transformation is molecularly heterogenous; would it be feasible to study cases and try to guide therapy? Currently we treat largely one size fits all.
- Dr Brian Link: Well done long term QOL methodology will be needed to sort out the relative utility of many of these options
- Dr. Andy Evens brings up the importance of overall survival in frontline FL studies, but Drs. Laurie Sehn and Judith Trotman point out the difficulty in measuring this front line. The determination of an acceptable surrogate is important that helps us understand the tradeoffs between PFS and acceptable toxicity

Session V: Discussion and Roadmap Creation

Dr. Andrew Zelenetz led the final discussion, asking the assembled experts how best to address the questions posed today, to improve our understanding of the disease and ultimately improve patient outcomes?

The following larger themes were discussed:

- How can we better understand the founder clone/CPC to try to identify it and develop targeted treatments for it? This could also lead to a better understanding of transformation.
- How can we better understand the microenvironment of FL? Does the tumor cell create its own microenvironment or does the microenvironment create the cell? Understanding this interplay will help develop better treatments and also help understand the impact on patients' overall immune system.
- Who are the patients who develop POD24? Can we develop robust predictors of POD24 and should we be actively looking for it in asymptomatic patients? How else can we risk-stratify patients?
- Can we utilize existing resources such as EPIC and LEO to develop large-scale epidemiologic data to help risk-stratify patients?

Research Priorities Roadmap

Disease Biology and Prognostic Factors (Session I)

- Mutations are common in the dominant transformed FL clone and affect regulators of the cell cycle, DNA damage response, and proliferation, as well as genes involved in immune evasion, but robust genetic predictors of transformation are lacking.
- The immunobiology of the tumor microenvironment in FL suggests an ineffective immune response to the malignant cells and the interplay between FL and T-cells, macrophages, and APCs including immune check-points is an area ripe for study.
- Early clinical progression is currently the most consistent predictor of a poor outcome in FL and a clearer understanding of genetics and biology as predictors for early progression is a crucial area of research for FL.

Risk Factors (Session II)

- The long-term immune function of patients is a manageable and important aspect of post-treatment survival that is both impacted by and impacts therapy.
- Collecting serial samples from clinical trials over time and/or utilizing existing large-scale genetic studies could help us search for risk factors, and analyze long-term outcomes such as immune function.
- Combining epidemiological studies with studies of epigenetic studies of tumor and microenvironment could also provide a better understanding of how risk factors and the microenvironment may affect each other.

Transformed Disease (Session III)

- Transformation events in follicular lymphoma are infrequent but account for a disproportionate amount of FL-related mortality.
- Standardized operational definitions of transformation would aid the systematic study of this phenomenon across cohorts and investigational teams.
- Similar to lymphomagenesis, genetic events in transformation appear to be sequenced and develop in a branching pattern from common precursor cells.
- As yet, no obvious genetic driver of transformation is identified – thus no unique biologic target for therapy development. Identification of such would be desirable.
- Identifying patients at risk for or in early stages of transformation (and other identifiers of "high risk") would also be desirable.

Current and Emerging Treatment Strategies (Session IV)

- The landscape of treatment options is broad, but there is no clinical or biologic data supporting a specific regimen nor a specific sequence. Development of a precision approach is needed to optimize the balance of risk and benefit to individual treatments.
- In the frontline setting, we need new criteria to select treatment (not just GELF)
- In the frontline setting, development of predictive biomarkers is needed
- Given long expected survival, there is a need to develop relevant clinical trial endpoints
- In the relapsed setting, it is difficult to compare across trials as the populations are very heterogeneous and number of relapses alone does not reflect disease refractoriness. Need harmonization/definition of types of relapses for clinical trial purposes
- In both the treatment-naïve and rel/ref settings, there is a need for predictive biomarkers of response and resistance for risk-stratified approaches

  There is a need to identify POD24 patients at diagnosis

Lymphoma Research Foundation Follicular Lymphoma Discovery Meeting

Tuesday, June 30, 2020 · 11 am – 4 pm ET

11:00 am **Welcome and Opening Remarks**
Andrew D. Zelenetz, MD, PhD
Memorial Sloan Kettering Cancer Center
Chair, LRF Scientific Advisory Board

11:15 am **Session I: Disease Biology and Prognostic Factors in Follicular Lymphoma**
Session Chairs:

Stephen Ansell, MD PhD
Mayo Clinic, Rochester

Laura Pasqualucci, MD
Columbia University H. Irving Comprehensive Cancer Center

John M. Timmerman, MD
UCLA Jonsson Comprehensive Cancer Center

12:15 pm **Session II: Risk Factors**
Session Chairs:

John P. Leonard
N*ewYork-Presbyterian Hospital*
Weill Cornell Medicine

Lindsay M. Morton, PhD
National Cancer Institute

Additional Presenters:

James Cerhan, MD
Mayo Clinic, Rochester

Christopher Flowers, MD, MS
MD Anderson Cancer Center

1:15 pm **Break**

1:30 pm **Session III: Transformed Disease**
Session Chairs:

Brian K. Link, MD
University of Iowa

Laura Pasqualucci, MD
Columbia University H. Irving Comprehensive Cancer Center

Additional Presenters:

Joe Schroers-Martin, MD
Stanford University

2:00 pm **Session IV: Current and Emerging Treatment Strategies**
Session Chairs:

Ranjana Advani, MD
Stanford Cancer Institute

Sonali M. Smith, MD
The University of Chicago
Chair-Elect, LRF Scientific Advisory Board

John M. Timmerman, MD
UCLA Jonsson Comprehensive Cancer Center

3:15 pm **Break**

3:30 pm **Session V: Discussion and Roadmap Creation**
All

4:00 pm **Closing Remarks**

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