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Proceedings of the Transformed Lymphomas Scientific Workshop

A Lymphoma Research Foundation Publication

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Introduction

Histologic transformation occurs when chronic lymphocytic leukemia (CLL) or an indolent non-Hodgkin lymphoma become aggressive lymphomas both clinically and morphologically. Transformed disease is often clinically associated with rapid progression, development of systemic symptoms, and has a poor prognosis. However, the underlying biology of transformation is not fully understood; the relative rarity of transformation, heterogeneity of transformation events, and the limited resources and related clinical trials dedicated to this patient population support the need for a platform through which experts in the field may discuss research findings and opportunities for collaboration.

The Lymphoma Research Foundation proposed to provide such a platform and developed the Transformed Lymphomas Scientific Workshop in August 2021, bringing together the world's leading lymphoma and CLL researchers and regulatory experts to discuss the latest research findings, receive updates on the progress of relevant clinical trials, and create a research agenda which, in turn, could prioritize research and clinical trials dedicated to transformed lymphomas, and ultimately enhance our understanding of transformation and improve patient care.

This white paper reflects the current state of research and the key elements of the Workshop discussion. Hematologists, oncologists and other healthcare providers are encouraged to consult the most recent guidance from national and federal healthcare agencies when making treatment recommendations. Patients should consult with their own healthcare providers when making treatment decisions.

The Foundation would like to thank the notetakers for this meeting and their contribution to this paper:

Madhav Seshadri, MD, Weill Cornell Medicine

Joo Song, MD, City of Hope Comprehensive Cancer Center

Sam Yamshon, MD, Weill Cornell Medicine

Meghan Thompson, MD, Memorial Sloan Kettering Cancer Center

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Panel Participants

Attendees and Workshop Faculty

Ranjana	Advani[2,3,4]	MD	Stanford University
Rajat	Bannerji[4]	MD, PhD	Rutgers Cancer Institute of New Jersey
Elias	Campo[4]	MD, PhD	Hospital Clinic Barcelona, University of Barcelona
Bruce	Cheson[1,3,4]	MD, FACP, FAAAS	LRF Scientific Advisory Board
Matthew	Davids[4]	MD, MMSc	Dana-Farber Cancer Institute
Christopher	Flowers[3]	MD, MS	MD Anderson Cancer Center
Elaine	Jaffe	MD	National Institutes of Health
Swetha	Kambhampati	MD	City of Hope
Manali	Kamdar[4]	MD	University of Colorado Health
Jeremiah	Karrs	DO	National Cancer Institute
David	Kurtz	MD/PhD	Stanford University
John	Leonard[3]	MD	Weill Cornell Medicine
Ryan	Lynch	MD	Fred Hutchinson Cancer Research Institute
Sami	Malek	MD	University of Michigan Medical School
Elisa	Mandato	PhD	Dana Farber Cancer Institute
Peter	Martin[3]	MD	Weill Cornell Medicine
Anthony	Mato[1,4]	MD, MSCE	Memorial Sloan Kettering Cancer Center
Joanna	Meehan-Rhodes	MD	Northwell Health
Ari	Melnick[2,3,4]	MD	Weill Cornell Medicine
Mark	Murakami	MD, MMSc	Dana Farber Cancer Institute
Loretta	Nastoupil[4]	MD	MD Anderson Cancer Center
Yasodha	Natkunam	MD, PhD	Stanford University
Susan	O'Brien[4]	MD	University of California Irvine Health and UCI
Jessica	Okosun[4]	FRCPath, PhD	Barts Cancer Institute, QMUL, London, UK
Neval	Ozkaya	MD	National Institute of Health
Erin	Parry	MD, PhD	Dana Farber Cancer Institute
Laura	Pasqualucci[3,4]	MD	Columbia University Institute for Cancer Genetics
Benedikt	Pelzer	PhD	Weill Cornell Medicine
Stefania	Pittaluga	MD, PhD	National Institute of Health
Kanti	Rai[2,3,4]	MD	Northwell Health
Joanna	Rhodes	MD	Northwell Health
Jason	Romancik	MD	Emory Winship Cancer Institute
Mark	Roschewski	MD	National Cancer Institute
Davide	Rossi[4]	MD, PhD	Oncology Institute of Southern Switzerland
Annapurna	Saksena	MD	The University of Texas at San Antonio
Gilles	Salles[4]	MD, PhD	Memorial Sloan Kettering Cancer Center
Pamela	Seam	MD	Kaiser Permanente Gaithersburg Medical Center
Margaret	Shipp[2,3,4]	MD	Dana-Farber Cancer Institute
Tanya	Siddiqi[4]	MD	City of Hope
Grace	Smith	MD	MD Anderson Cancer Center
Sonali	Smith[1,3,4]	MD	University of Chicago
Deborah	Stephens	DO	The University of Utah
Paolo	Strati	MD	MD Anderson Cancer Center
Nicole	Sunseri	MD	University of Chicago
Saber	Tadros	MD	National Cancer Institute
Catherine	Thieblemont[4]	MD, PhD	Hôpital Saint-Louis, Fernand-Widal
Chaitra	Ujjani	MD	University of Washington Medicine
Yucai	Wang	MD, PhD	Mayo Clinic

Panel Participants (continued)

Guido	Wendel	MD	Memorial Sloan Kettering Cancer Center
Bonnie	Yanbo Sun	PhD	Dana-Farber Cancer Institute
Kristena	Yossef	MD	Geisinger Health System
Roberta	Zapposodi	PhD	Weill Cornell Medicine
Andrew	Zelenetz[3,4]	MD, PhD	Memorial Sloan Kettering Cancer Center
Pier Luigi	Zinzani[4]	MD, PhD	University of Bologna
Ting	Zhou	PhD	Memorial Sloan Kettering Cancer Center

Notetakers

Madhav	Seshadri	MD	Weill Cornell Medicine
Joo	Song	MD	City of Hope
Sam	Yamshon	MD	Weill Cornell Medicine
Meghan	Thompson	MD	Memorial Sloan Kettering Cancer Center

Pharmaceutical Industry Attendees

Kamal	Chamoun	MD	Karyopharm
Robert	Chen	MD	AstraZeneca
Anita	Gandhi	PhD	Bristol-Myers Squibb
David	Hyman	MD	Loxo Oncology at Lilly
Ginna	Laport	MD	Genentech
Roula	Qaqish	PharmaD	AbbVie
Ken	Takeshita	MD	Daiichi Sankyo

Regulatory Agency Attendees

Mona	Elmacken	MD	US Food and Drug Administration
Nicole	Gormley	MD	US Food and Drug Administration
Chatchada	Karanes	MD	US Food and Drug Administration
Yvette	Kasamon	MD	US Food and Drug Administration
Steven	Lemery	MD	US Food and Drug Administration
Margret	Merino	MD	US Food and Drug Administration
Candis	Morrison	PhD, CRNP	US Food and Drug Administration
Kavita	Natrajan	MD	US Food and Drug Administration
Helka	Peredo-Pinto	MD	US Food and Drug Administration
Nicholas	Richardson	DO, MPH	US Food and Drug Administration
Maryam	Sarraf Yazdy	MD	US Food and Drug Administration

Lymphoma Research Foundation Guests

Jeff	Block		LRF Board of Directors
Julie	Dodd	MD	Follicular Lymphoma Foundation
David	McCullagh	BS, MBA	Jaime Peykoff Follicular Lymphoma Initiative
Kristen	Venick	MSN	Niagra Cares

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1. Transformed Lymphomas Workshop Steering Committee Co-Chair
2. Transformed Lymphomas Workshop Steering Committee Member
3. Lymphoma Research Foundation Scientific Advisory Board Member

*Transformed Lymphomas Workshop Faculty/Moderator/Panelist

Presentations

Introductory remarks were given by Kanti Rai, MD, Northwell Health, and Sonali Smith, MD, University of Chicago, both members of the Lymphoma Research Foundation (LRF) Scientific Advisory Board.

Dr. Rai noted that Richter transformation was first described in 1928 by Maurice Richter as the development of an aggressive large cell lymphoma in a patient with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Over intervening decades, progress has been made in the treatment of lymphoma and CLL/SLL due to advances in science and technology. Despite this progress, the inability to successfully treat many patients with transformed disease remains. Experts in the field fully recognize that this gap exists; the Transformed Lymphomas Scientific Workshop, convened by the LRF, is necessary to address this critical unmet need.

Dr. Smith expressed gratitude and excitement that numerous global thought leaders have gathered to discuss ways in which to address the challenges of transformed disease. She cited a 1942 paper, among the first published accounts of transformed follicular lymphoma, further demonstrating how little is known about transformation and the challenges facing the field and Workshop participants in the interval decades. She shared recent data regarding disease biology and patient outcomes and outlined the Workshop objectives including fostering discussion, debate and dialogue among the international lymphoma community, and determining next steps for further investigation.

Session I: Disease Biology

The Disease Biology Session, moderated by Ari Melnick, MD, Weill Cornell Medicine highlighted the molecular and genetic features of transformed lymphomas as well as pathways that may represent potential targets in future therapeutic approaches.

Davide Rossi, MD, PhD, Oncology Institute of Southern Switzerland, presented on transformed chronic lymphocytic leukemia (CLL) and Richter Transformation (RT)[1]. RT is the transformation of CLL into an aggressive lymphoma; the vast majority of RT cases transform to diffuse large B-cell lymphoma (DLBCL) which is why the research in this area is primarily focused on DLBCL. Less than 10% of cases transform to Hodgkin lymphoma (HL), by comparison. Approximately 80% of DLBCL cases in patients with CLL are clonally related to the CLL and are associated with poor outcomes. The remaining 20% have clonally unrelated DLCBL and share commonalities, including prognosis, with *de novo* DLBCL when similarly treated.

Studying RT remains challenging due to the variable histologic criteria, as well as a lack of cell line and mouse models. The progression to transformation in RS is likely to be linear with trisomy 12 (+12) and *NOTCH1* mutations, with additional abnormalities such as *BCR* mutations, unmutated IGHV, reliance on subset 8[2] for the BCR stereotype and then ultimately genomic instability related to genes such as *CDKN2A*, *TP53*, and *MYC*. *TP53* mutation is frequently seen in RT. Cases with the usage of subset 8 for BCR may be a group that can be treated with BCR inhibitors (BTK inhibitor). Another possible approach is focusing on the immune suppressive microenvironment with new agents. CAR-T cell therapy may also be an option especially if one is able to address the exhausted T cells that are typically seen in the microenvironment of RT.

Laura Pasqualucci, MD, Columbia University Institute for Cancer Genetics, presented on transformed follicular lymphoma (tFL). The clonal evolution of the disease is likely divergent from a common precursor cell that gains alterations such as loss of B2M, *ASHM, MYC* deregulation, loss of *TP53* or *CDKN2A*. The transformation is primarily a genetic event in conjunction with epigenetic and microenvironment changes. The dominant tFL clone can be identified by sensitive methods in pre-clinical settings Similarities with RT can be seen with transforming events such as MYC deregulation and TP53 or CDKN2A abnormalities, but these are not necessarily predictive of transformation to DLBCL. At this time, we are currently unable to predict those patients who will progress to tFL; however, it has been established that *CREBBP* and *KMT2A* mutations are early events. Targeting the common progenitor cell may be needed with a focus on the CREBBP/KMT2D dependencies in this disease.

Session II: Diagnosis and Prognosis

The Diagnosis and Prognosis Session was moderated by Margaret Shipp, MD, Dana-Farber Cancer Institute, and reviewed the incidence and classification of transformed lymphomas, diagnostic criteria, clinical behavior, and outcomes.

Elias Campo, MD, PhD, Hospital Clinic Barcelona, University of Barcelona, presented on transformed CLL (RT), which occurs in 5% of patients with CLL. RT may have diverse clinical and biological underpinnings (including clonally related versus not clonally related scenarios) with important implications for treatment and prognosis. It is important to obtain pathological confirmation of RT verified by an expert hematopathologist as a number of entities can mimic RT. It is associated with an aggressive course of disease and poor prognosis. As stated in Session One, RT is histologically similar to DLBCL in approximately 90% of cases and to HL in approximately 10% of cases.[3] The DLBCL type of RS is characterized by proliferative centers similar to CLL, but areas with large cells are also seen. CD23 and CD5 positivity are variable and are not helpful in determining if the DLBCL is clonally related to the pre-existing CLL. Proliferation as measured by Ki67 is typically high. HL-like RS is characterized by clusters of histiocytes and on higher magnification Reed-Sternberg or Hodgkin cells are seen. Importantly, examination of the microenvironment is required to establish the diagnosis. The immunophenotype of HL arising from CLL is similar to primary HL, although Epstein-Barr virus (EBV) is more common in transformed cases.

Risk factors for RT include germline genetic characteristics, including the BCL2 GG genotype, CD38 GG genotype, and LRP4 TT genotype. Somatic mutations found in CLL cells associated with RT include unmutated IGHV, stereotyped BCR receptor (subtype 8), trisomy 12, NOTCH1 mutations, TP53 mutations, c-MYC expression, CDKN2A deletion, and others, as well as complex karyotype or major structural abnormalities. Clinical factors associated with RT include bulky lymphadenopathy, Rai stage III-IV disease, and prior treatment with purine analogs or alkylating agents.

RT must be distinguished from a number of other entities with similar clinical presentations. The first is EBV-related lymphoproliferative disorders (LPDs). These are characterized by large cells, sometimes with pathology consistent with HL. Usually these are clonally unrelated to the pre-existing CLL, and have been described most often in patients previously treated with fludarabine. A subset of these cases may regress spontaneously, although most cases require systemic therapy. The second is accelerated CLL, a recently recognized entity which can mimic large cell transformation in its clinical presentation. Pathology of accelerated CLL often has highly expanded proliferative centers with a high rate of proliferation. It is important to distinguish accelerated CLL from RT as these diseases are managed differently and may have different prognoses; patients with accelerated CLL may respond to venetoclax or other targeted agents, while those with true RT require a different strategy with typically worse outcomes regardless of treatment. Circulating malignant cells may exhibit a morphology or other characteristics of prolymphocytic transformation. Accelerated CLL confers a poor prognosis, and the underlying biology remains is unclear thus far. The third entity is pseudo-transformation. This phenomenon can be seen in patients for whom Bruton tyrosine kinase (BTK) inhibitor therapy is discontinued. Following discontinuation, nodal enlargement can be seen with highly proliferative centers with large cells suggestive of DLBCL. However, when BTK inhibitor therapy is resumed, these lymph nodes regress and follow up studies after several months of therapy again show findings typical of CLL. This phenomenon is associated with unmutated IGHV status and the presence of *TP53* mutations and is typically encountered in patients who have received multiple lines of therapy. It is important to recognize this entity as it has important implications in treatment and prognosis. Treatment with BTK inhibitor therapy, most commonly ibrutinib, has led to atypical histologic transformation (HT) patterns. Terminal or plasmablastic differentiation of CLL during ibrutinib therapy has been observed, as well as transdifferentiation of CLL to a histiocytic sarcoma, of myeloid lineage. In both of these cases the transformed hematological malignancy was clonally related to the initial CLL. This observation suggests that the selective pressure of ibrutinib may drive the CLL towards a lineage not dependent on BTK- or BCR-pathway signaling.

Matt Davids, MD, MMSc, Dana-Farber Cancer Institute, presented on the clinical and radiographic features of RS. It is unclear whether the increased use of targeted agents such as ibrutinib, venetoclax, and idelalisib impacts the risk of transformation of CLL even as they may impact the biologic process as discussed above. In the chemoimmunotherapy era, the risk was approximately 4-5%. More recent studies in the last decade, which witnessed increased use of targeted agents, showed a similar rate of 3.9%. It is difficult to determine with certainty at this point, but with increased use of these novel agents and longer follow up it will become clear how these agents affect the rate of transformation.

RT should be suspected when a patient with CLL shows a rapid physical deterioration, new B-symptoms such as fever, rapid or discordant progression of lymphadenopathy, or a rapid rise in lactate dehydrogenase (LDH). Histologic confirmation is mandatory; this should be PET-guided for targeting of the most FDG-avid lymph node to increase sensitivity. Determination of the genetic basis for the transformation and comparison of clonal relationship between the aggressive lymphoma and the prior CLL may affect prognosis and treatment.

The role of PET-CT in predicting the risk of RT or determining if RT has occurred is unclear. Retrospective series of patients treated in the chemoimmunotherapy era showed that maximum standard uptake value (SUVmax) of >10 was highly predictive of RT, and SUVmax 5-10 gave greater than 90% sensitivity and specificity to detect patients who would have RT. Conversely, another more recent study showed that among patients treated with BCR pathway inhibitors, PET-CT was less helpful in predicting RT, with SUVmax >10 giving sensitivity of 71% and specificity of 50%, with a positive predictive value of only 26%. The utility of PET-CT in predicting RT in patients treated with targeted therapy therefore appears to be limited. Use of imaging in prognostication is an ongoing area of research. One study of patients with CLL showed that pretherapy TMTV of greater than 1200 cm3 was associated with poorer survival and higher risk of RT. Although no disease modifying therapy has yet been identified for patients deemed to be at high risk of RT, our ability to risk stratify patients may nevertheless be clinically useful for monitoring and early recognition as well as for clinical trial design.

Once RT occurs, prognosis is poor. SEER data show that survival for RT is much poorer than for de novo DLBCL, underscoring that these are different diseases with distinct underlying biology. Median overall survival (mOS) of RT in prospective studies is approximately 8-9 months; however, in a retrospective study of real-world data, median OS was 3.3 months. Much of these data comes from patients treated with multiple lines of therapy prior to the widespread use of targeted agents; thus, it is unclear if these agents would alter the disease course. Although prognosis is generally poor, several factors may help to risk stratify patients with RT. HL generally has a better prognosis than DLBCL type RS, and several clinical factors associated with a better prognosis have been identified including ECOG <2, normal LDH, platelet count >100, tumor size <5 cm, <1 prior therapy, and absence of clonal relationship between the aggressive lymphoma and the concurrent CLL.

Jessica Okosun, MA, MB, Bchir, MRCP, FRCPath, PhD, Barts Cancer Institute, QMUL (London) presented on tFL. As with RS, there are ongoing efforts to understand the biology of this disease, and to identify patients who are at risk for transformation. Transformed FL is likely a heterogenous disease. The histology is frequently similar to DLBCL; however, the incidence of various subtypes of tFL has not been well characterized: for example, by cell of origin (germinal center derived or activated B-cell type), double or triple hit, high grade or Burkitt-like. Atypical phenotypes have been observed including de-differentiation into a TdT+ lymphoblastic lymphoma and transdifferentiation to histiocytic or dendritic cell neoplasms. In both of these cases the *t(14;18)* translocation was seen consistently with the pre-existing FL, indicating a clonal relationship. Large-scale population data characterizing the histologic subtypes of tFL will be an important area of research going forward to better characterize this heterogeneous disease, a requisite to rational design of novel therapeutic strategies.

The true risk of transformation in FL is unclear. Some sources state that transformation of FL is relatively common, with a risk of 2-3% per year for the first 15 years after diagnosis. Outcomes following transformation are historically poor with median OS between 12-24 months. Accordingly, tFL accounts for a significant portion of mortality

associated with FL. A challenge in determining the incidence of transformation is the possibility that not all tFL cases are captured, as biopsy at the time of progression of FL is not routinely done. In the PRIMA trial, 42% of patients with progression of disease underwent biopsy, of whom 21% were found to have tFL. In the ARISTOTLE trial 21% of patients with progression of disease underwent biopsy, of whom 50% were found to have transformation. Based on these data it is likely that transformation is more common than is currently recognized, but diagnoses are limited by underutilization of repeat biopsy at the time of progression of disease.

Although treatment of FL is historically not thought to impact the risk of transformation, data suggest that rituximab may reduce the risk of transformation. In the pre-rituximab era, the risk of transformation of FL was approximately 30% at 10 years; however, in the rituximab era most studies show approximately 8-9% risk of transformation at 10 years. It is therefore possible that, among patients who have an indication for treatment, rituximab may decrease the risk for transformation, although it does not eliminate this risk entirely.

Significant gaps in understanding this disease and its management exist. It remains to be seen if the risk for transformation can be reduced further with novel therapeutic combinations. It is also unclear if a subgroup of patients with FL who are at high risk for transformation can be identified early, and if so, can early treatment prevent transformation. Many clinical, radiologic, and genetic or biologic factors are available to stratify patients into risk groups. Although these factors may predict risk of progression and mortality of patients with FL, they are not routinely used to predict the risk of transformation. Independent risk factors for transformation have been identified. These include clinical factors such as age, histologic grade, high risk FLIPI, and elevated LDH; genetic factors including *TP53* mutations, BCL2 expression; and microenvironmental factors including FOXP3 expression and enrichment of FOXP1 or NF-kB gene signatures. These factors have not yet been demonstrated to adequately estimate risk of transformation in the clinical setting and have not been incorporated into routine clinical practice.

Numerous barriers exist to identifying biomarkers for predicting tFL. Although gene expression signatures associated with tFL have been identified, it is difficult to capture these clones at the time of diagnosis. Genomic analyses at the time of progression or transformation are also limited by the number of biopsies being performed and the quality of samples available. The limited samples coupled with the heterogeneity of disease in time and space limits the ability to capture pathology at critical times in the course of disease. One possible way to overcome this problem may be circulating tumor DNA (ctDNA), a less invasive way to assess to compare genomic diversity at the time of diagnosis with the time of transformation. Doing so could identify tFL-specific mutations which might be used to monitor response to therapy as well. Overall, there are still major unmet needs in our ability to predict patients who will transform, and to discover new strategies to potentially mitigate this risk.

Manali Kamdar, MD, University of Colorado Health, presented on transformed marginal zone lymphoma (MZL), a rare disease with limited epidemiological data. Risk for transformation is estimated at approximately 2.4% per year, although there is a broad range of estimates across studies. Approximately 5% of patients will undergo histologic transformation (HT) at 5 years, 8% at 10 years, and 10% at 12 years, and the median time to transformation is 30 months. HT occurs at similar rates across MZL subtypes: 5% with splenic MZL (SMZL), 4% for mucosal-associated lymphoid tissue (MALT) type, and 3% in nodal MZL (NMZL). Although HT appears rare, it has a poor prognosis, particularly earlier in the disease course. Transformation within 1 year of diagnosis of MZL is associated with 4-year OS 43%, while transformation after 1 year from initial diagnosis is associated with 4-year OS 84%.

Transformed MZL (tMZL) should be suspected in patients who have a sudden clinical deterioration, rising LDH, rapidly progressive lymphadenopathy, B-symptoms, or hypercalcemia. The diagnosis requires sheets of large cells comprising at least 20% of the neoplastic population in a background of indolent lymphoma. Clonality should be demonstrated; in usual clinical practice this is done by assessment of light chain restriction by flow cytometry and immunohistochemistry. Transformed MZL is usually characterized by DLBCL, mostly non-germinal center B-cell type, sometimes double expressor. Transformations to HL or Burkitt lymphoma have been reported, but are rare. False positive diagnoses are possible as approximately 20-50% of MZL cases have larger centroblasts interspersed

among lymphoma cells, leading to an erroneous diagnosis of transformation. It is important to obtain expert hematopathologist review for suspected transformed MZL.

Clinical and biologic prognostic factors define high risk MZL. For extranodal MZL (ENMZL), poor prognostic factors include an increased MALT-IPI, progression of disease within 24 months of diagnosis (POD24), involvement of multiple mucosal sites, CD5 positivity, and elevated serum Beta-2 microglobulin. In addition, strong FOXP1 staining, trisomy 3 or trisomy 8, gastric upregulation of chemokine receptors, and *TP53* deletion have been associated with poorer survival in patients with ENMZL. The site of involvement may predict likelihood of transformation; gastric or head and neck ENMZL confer a lower risk of transformation, while liver involvement and HCV infection confer a higher risk. In patients with NMZL, MALT-IPI, poor performance status, and CD5 positivity have been associated with poor prognosis. A higher incidence of del(20q12) is seen in transformed NMZL, and in one series, all patients with HT had bone marrow and lymph node involvement. Other risk factors for transformation are not well defined. In SMZL, risk factors for HT include *TP53* mutations, *NOTCH2* mutations, deletion of 7q, and *TNFAIP3* mutations. Presence of an M-protein and greater peripheral lymph node involvement were also associated with HT.

The site of transformed disease may also be prognostic. Occurrence of transformation in the bone marrow was associated with a poorer prognosis in tSMZL, while occurrence in the lymph nodes, spleen, or extranodal sites was associated with greater survival. Chemotherapy or splenectomy do not affect risk for HT in SMZL. In a study of tMZL from 1995-2016 identified other factors associated with HT prognosis as well, including involvement of greater than 4 nodal sites and failure to achieve CR after first line treatment.

The use of PET-CT in MZL is controversial due to the variability of FDG avidity, and limited data. One study showed that SUVmax >10 was associated with a high rate of HT (20% vs 5%). In a study of 40 patients with HT, 11 from MZL, showed that SUVmax >10 predicted HT with 80% certainty, while SUV >13 predicted HT with 90% certainty. Although the role of PET-CT alone in diagnosing HT is unclear, it can be used to guide biopsy to maximize sensitivity. TMTV and other imaging-based risk assessments have yet to be explored in transformed MZL. Few prospective studies have evaluated treatment for patients with tMZL. In one study, treatment naïve patients had a CR rate of 91% with standard frontline DLBCL-based regimens without the need for autologous stem cell transplant.

A number of challenges exist in studying tMZL, especially the rarity and heterogeneity. These factors often lead to different subtypes being grouped together in studies. A collaborative research group and shared repository of paired biopsy samples at the time of diagnosis and at transformation would help overcome these obstacles and enable more comprehensive investigations. Another challenge is the paucity of tissue samples at the time of transformation. Re-biopsy at progression or when transformation is suspected should be performed more frequently both at academic centers and community practices. A third challenge is variability in disease course. Patients may have indolent disease for a long period of time before transformation, making prospective studies difficult. It may be more feasible to design a retrospective study of patients who have transformed lymphoma and to compare tissue samples and imaging obtained earlier in the disease course if possible.

Session III: Clinical Care and Standards of Care

The Clinical Care and Standards of Care Session was moderated by Ranjana Advani, MD, Stanford University, and reviewed the current treatment guidelines for transformed disease and the challenges associated with accurate diagnoses, referrals, and access to care.

Susan O'Brien, MD, University of California, Irvine Health, noted that RT should be clinically suspected in patients with rapid growth of lymph nodes, rapid clinical deterioration, fever in the absence of infection, and a rising lactate dehydrogenase. Diagnostic testing should include a PET CT scan and then biopsy of the disease site with the highest SUV. Importantly, clinicians must maintain a high level of suspicion for RT in patients with CLL because the diagnosis

can be missed if not considered in a timely manner. For example, it is possible that in the early trials of ibrutinib patients were enrolled and treated who had undiagnosed RT, and ibrutinib monotherapy would not be expected to work well in these patients.

Two major categories of treatment options have been studied in patients with RT: 1. Anthracycline-based regimens and 2. Platinum-based regimens. In general, complete response rates have been approximately 20% and there are many patients who do not have any response to initial therapy. Overall, the data available are from small series (15-35 patients), and regimens studied have included OFAR-2, R-CHOP, O-CHOP, R-hyper-CVAD, R-EPOCH, DHAP, ESHAP, R-hyper-CVAD and GM-CSF, Hyper-CVAD. The CR rates range from 6-38%. Toxicity during therapy and treatment failure due to poor performance status and advanced age is common problem in patients with RT as this patient population is often very sick at time of disease presentation. In summary, while disease resistance to therapy is perhaps the biggest obstacle with RT, poor performance status also plays a significant role and should be considered in clinical trial design and eligibility criteria.

In summary, the prognosis for patients with RT is dismal. Chemoimunotherapy (CIT) has a mediocre overall response rate and complete responses occur in a minority of cases. Treatment associated toxicity can be high, and patients are often heavily pre-treated and may be symptomatic at the time of RT diagnosis. There are several unanswered questions regarding RT, particularly in the era of novel targeted agents. It is unknown whether the addition of small molecules to CIT will improve outcomes. Additionally, will the declining use of CIT for the treatment of CLL result in a lower incidence of RT? It is also not yet known whether RT arising in patients who have only received novel targeted agents (as opposed to prior CIT) will have a different prognosis when treated with CIT for RT. Clinical trials examining novel therapeutic approaches are needed to answer these questions and improve outcomes for patients.

Gilles Salles, MD, PhD, Memorial Sloan Kettering Cancer Center, addressed tFL. In patients with tFL, there is a higher risk of lymphoma-related death, the predominant causes of death for these patients. In contrast, in the absence of transformation, the risk of death for follicular lymphoma patients is quite low and causes of death are almost equally distributed between lymphoma-related death, deaths unrelated to lymphoma, and unknown causes. Additionally, data from the PRIMA study demonstrate that among early progressors, histologic transformation is a common event. Among biopsies taken during the first year of follow-up, 37% demonstrated transformed disease; these biopsies represented over half (58%) of cases of histologic transformation. Additional data for patients with FL treated with bendamustine and rituximab (BR) show that transformation may be an early event, with 10% of BR-treated patients in the study having tFL with a median time to transformation of 8.4 months. The 2-year overall survival (OS) following transformation was 40%.

Additional studies demonstrate that survival outcomes for patients with tFL are poor and worsen over time. For example, in one series, at a median follow-up of 4.6 years, the survival after tFL was 41% (36-46) at 5 years and 32.5 (25-38%) at 10 years. Over half of the causes of death were due to disease progression (53%) and unknown causes represented another 34% of deaths. Whether tFL and FL are diagnosed concurrently or sequentially also appears to impact outcomes. Danish registry real-world data show that patients with simultaneous diagnosis of tFL and FL have better outcomes (more comparable to DLBCL outcomes) compared to patients with sequentially transformed FL, especially if there is treatment for the prior indolent component. Interestingly, tFL patients with confirmed pathology-proven transformation had a similar outcome to FL patients with clinically suspected transformation (e.g., patients with rapid disease growth, high LDH, etc. but without histologically proven disease. This was also found in the PRIMA study.

Additional factors appear to predict survival including timing of diagnosis of the transformation and prior therapies. The survival outcomes of patients diagnosed with transformation earlier in the disease course are worse. In a series from the Mayo clinic and Iowa, survival was significantly inferior for patients diagnosed earlier in the disease course (diagnosed with tFL <18 months from the initial FL diagnosis) and for patients who had received R-CHOP for FL treatment prior to the diagnosis of tFL. Additionally, patients exposed to prior chemotherapy for treatment of FL

prior to tFL have been shown to have worse outcomes than those receiving chemotherapy after tFL diagnosis. Alternatively, there were not differences in survival outcomes for patients who received treatment with rituximab before or after the diagnosis of tFL.

Given that there are limited data from clinical trials and retrospective series, most guidelines for the treatment of tFL are based on expert opinion. The NCCN guidelines recommend that for patients with tFL without "double hit" histology and minimal or no prior chemotherapy exposure, anthracycline-based chemotherapy (e.g., R-CHOP chemotherapy) should be used. For patients with tFL to "double hit" DLBCL, the NCCN guidelines for high-grade B-cell lymphoma with translocations of *MYC* and BCL2 and/or *BCL6* should be followed (NCCN guidelines). For patients with tFL with histologic transformation to DLBCL after multiple prior lines of therapy, the NCCN guidelines list several options including: clinical trials, anti-CD19-directed CAR T-cell therapy if 2 or more prior CIT regimens have been administered, polatuzumab vedotin +/-bendamustine +/- rituximab, other CIT regimens +/- ISRT, ISRT or selinexor (after at least 2 prior lines of systemic therapy). Best supportive care is also an option. Prior treatments should be considered when selecting the most appropriate line of therapy (NCCN guidelines). For patients with multiple prior lines of therapy, another question is whether these patients should receive consolidation with high dose chemotherapy with autologous stem cell rescue plus or minus involved site radiation therapy. The roles of allogeneic stem cell transplant and CD19-directed CAR T-cell therapy are also uncertain.

One proposed treatment algorithm explores two groups of patients: CIT-naïve tFL patients and CIT-exposed tFL patients. For CIT-naïve tFL patients, the recommendation is to treat similarly to de novo DLBCL. There are no data to support rituximab maintenance or consolidative autologous transplant in the tFL setting. For tFL patients with prior exposure to CIT and DLBCL histology, treatment depends in part on prior therapy, particularly whether or not the patient has received a prior anthracycline-based regimen. If the patient is anthracycline naïve, then typically R-CHOP is administered and a consolidative autologous stem cell transplant may be considered if the patient has a response to CIT. For patients with prior anthracycline exposure, salvage chemotherapy is given followed by consideration of consolidative autologous stem cell transplant if the patient responds to chemotherapy. Third-line treatment options include CAR T cell therapy, clinical trials, alternative CIT regimens, supportive care or allogeneic stem cell transplant. For patients with high-grade DLBCL histology, a similar treatment approach has traditionally been used. However, outcomes for high-grade transformed lymphomas have been historically poor. Therefore, investigational agents and early CAR T-cell therapy referral should be considered for high-grade histology patients.

A subgroup of tFL patients have poor responses to treatment. In the PRIMA study, among patients with biopsy-proven histologic transformation, 28.2% had progressive disease as the best response to salvage therapy. More data are needed regarding the sequencing of R-CHOP following BR prior to make a recommendation about whether the risk of transformation should influence the first-line therapy of FL (e.g., whether the anthracycline should be saved until the patient experiences transformation).

There is limited information regarding the role of high dose chemotherapy with autologous stem cell transplant (ASCT) as consolidation in patients with tFL. Data from the PRIMA study demonstrate that outcomes are superior for patients who receive ASCT after transformation compared to those that do not undergo ASCT. In a propensity-matched analysis for ASCT for patients in CR1, 49 patients went on to get a transplant versus 98 patients who did not. There was a PFS benefit to transplant (HR 0.5, p=0.043) but no significant OS benefit. However, it should be noted that the overall survival analysis should be interpreted carefully, as only 2 patients in the ASCT group went on to receive CAR T-cell therapy, while more patients in the non-ASCT group received CAR T-cell therapy which may impact overall survival outcomes. In terms of allogeneic stem cell transplant (alloSCT), there has been no study to show a significant difference when comparing ASCT versus alloSCT. There is emerging data to support the use of CD19-directed CAR T cell therapy in tFL; however, where CAR T-cell therapy should ultimately fit in the treatment paradigm of tFL remains uncertain.

In recent years, there have been several new agents approved for the treatment of relapsed and/or refractory DLBCL including polatuzumab vedotin and tafasitamab-lenalidomide. However, their clinical activity in tFL is largely unknown. Numerous studies highlight that novel approaches to large cell lymphoma may have a role in the treatment of tFL. However, further data specifically focused on indolent transformed lymphoma subgroups is required in clinical trials moving forward.

In conclusion, the approach to treatment of tFL is largely driven by expert opinion given the limited available data to guide tFL treatment. There is an unmet need for better therapies for patients with tFL. One approach to expand therapeutic options would be to study outcomes of standard NHL therapies in more patients with tFL.

Catherine Thieblemont, MD, PhD, Hôpital Saint-Louis Hôpitaux Universitaires Saint-Louis, Laboisière, Fernand-Widal, addressed MZL. The histology of tMZL includes DLBCL, Hodgkin and Burkitt-like subtypes. Diagnosis of tMZL is based on pathologic review of nodal biopsy and is characterized by large centroblasts among small cells. There is often P53 expression. Clinically, patients with tMZL may have rapid disease progression characterized by enlarging lymph nodes and elevated lactate dehydrogenase. PET CT often shows an increased SUV compared to indolent lymphomas (e.g., SUV >10-15), although there is no clear SUV cutoff to differentiate transformed versus indolent disease.

In general, tMZL has a lower incidence compared to tFL, and series demonstrate frequencies ranging from 3.8-11.6%. There is no clear relationship between the risk of tMZL and the type of underlying MZL subtype. In larger series, the median time from MZL diagnosis to tMZL is 1.9-4.5 years. The risk of transformation appears to be time dependent (higher incidence at 10 years compared to 5 years. Risk factors for the development of tMZL are elevated lactate dehydrogenase, the number of nodal sites (<4 or >4), and a lack of complete response with initial therapy. Overall, it appears that there are probably biological differences between tMZL subtypes.

There is no existing standard of care for tMZL. Notably, most clinical trials exclude patients with tMZL. There are only a few clinical trials with tMZL patients that identify these patients (3 clinical trials on clinicaltrial.gov as of 8/3/2021 compared to 35 registered trials for transformed indolent lymphomas). When tMZL patients are included on clinical trials, they are typically included in a heterogeneous group of transformed indolent lymphomas. Given differences in disease biology between various transformed lymphoma subtypes, this approach makes it difficult to draw conclusions. For example, in the trial of lisocabtagene-maraleucel there were 18 patients with transformed indolent lymphomas and 10 patients (4% of the overall population of included patients) with transformed marginal zone lymphoma. In contrast, the JULIET and ZUMA trials excluded tMZL patients altogether.

Treatment for tMZL has traditionally been anthracycline-based chemotherapy in combination with an anti-CD20 monoclonal antibody if the patient has not had prior anthracycline-based chemotherapy. The approach for patients with prior anthracycline exposure is less clear. Additionally, there are few data to guide whether high dose chemotherapy with autologous stem cell transplant (ASCT) should be used for consolidation for patients who have a response to initial chemotherapy.

In summary, there are many remaining questions in the management of tMZL. In particular, the role of high dose chemotherapy with ASCT is uncertain. Additionally, there are few data regarding cellular therapies including CAR T-cell therapy or targeted therapies or their combinations (e.g., BTK inhibitors, PI3Kis) in the treatment of tMZL. Enhanced biological understanding of tMZL as well as clinical trials that separately study tMZL may aid in the development of novel therapeutic approaches and improved clinical outcomes for these patients.

Many factors contribute to the lack of data to guide the management of transformed lymphomas including the relative rarity of the diseases and the fact that many trials, including those of DLBCL patients, exclude patients with transformed disease. Furthermore, while progress has been made in terms of the biological underpinnings of different transformed lymphomas, the trials that include transformed lymphoma patients often do not incorporate

the biological knowledge of specific transformed subtypes into the trial design. Additionally, in the era of targeted therapies (e.g., BTKis, PI3-kinase inhibitors), there will now be patients who have been treated with multiple targeted agents prior to transformation. The biology of transformed disease in patients with targeted therapy exposures may be different than the biology of transformed disease in patients who have only received CIT. This is an area for ongoing study as more patients are treated with targeted therapy-based approaches. Additionally, whether the initial treatments and sequencing of therapies for the underlying non-transformed disease impact what the subsequent treatment should be in the setting of transformation remains unknown. For RT specifically, for example, the fact that many trials require prior RT-directed therapy as eligibility criteria is a barrier to enrollment. First-line RT therapy is often ineffective and subsequently renders these patients quite ill at the time that they are eligible for clinical trials if prior RT-directed therapy is requirement.

With regards to different disease subtypes, there are many possible therapeutic approaches that may be explored. These include checkpoint inhibitor therapy, CAR T-cell therapy and bispecific antibody therapy for patients with RT. Additionally, for tFL patients, epigenetic mechanisms and MYC-targeted drugs should be explored as well as rational combination therapies. In tMZL, lenalidomide and BTKis have not yet been studied. Additionally, drugs targeting the immune microenvironment should be evaluated in transformed lymphomas.

When approaching the unmet need for patients with transformed lymphomas, a big question is whether to design separate trials for each subtype of transformed lymphoma versus a basket trial. Overall, given disease heterogeneity, the preference among experts is to have separate trials for each transformed subtype. However, issues with this approach include accrual and administrative barriers associated with opening individual trials versus a larger trial with multiple subgroups or arms. There is a clear consensus among experts that a multi-institutional approach is required given the limited number of patients at a single institution. Forming a consortium may prove helpful in organizing institutions to study transformed lymphomas.

Session IV: Clinical Trials, Part 1

The first Clinical Trials Session was moderated by Sonali Smith, MD, The University of Chicago, and highlighted relevant clinical trials and recent research findings from clinical investigators.

Prior to an extended panel discussion, Loretta Nastoupil, MD, MD Anderson Cancer Center, offered a presentation on New Agents and Transformed Lymphomas and Rajat Bannerji, MD, PhD, Rutgers Cancer Institute of New Jersey, offered a presentation on New Modalities and Transformed Lymphomas.

Dr. Nastoupil provided an overview of the current state of clinical trials, noting that rates of transformation have decreased in the rituximab era, but that there still remains room for improvement. Outcomes appear to be worse in patients who have transformations early in their course, and patients with prior anthracycline exposure also have inferior outcomes. While novel agents show promise, interesting data from MD Anderson Cancer Center showed that access to novel agents doesn't change outcomes in patients with RT. Heterogeneity in prior treatment courses makes it difficult for trials of patients with transformed lymphomas to determine eligibility criteria, which is a major barrier to trials in this population.

Loncastuximab teserine, an antibody-drug conjugate targeting CD19, enrolled patients with transformed disease as part of a single-arm phase II study and 20% of the total study population had transformed disease. Patients with prior allogeneic or autologous stem cell transplants as well as prior CAR T cell therapy were enrolled. Despite a population with refractory disease, overall response rate was 48% with a 24% rate of complete response. CC-99282 is a cereblon modulator that has shown efficacy in transformed lymphomas. While it is the latest of a number of immunomodulatory drugs in the class, it is notable because it appears to have efficacy irrespective of cell of origin.

Importantly, transformed follicular lymphomas are typically germinal center B-cell (GCB) lymphomas while novel agents generally appear to have efficacy in activated B-cell (ABC) subtypes, so efficacy in GCB lymphomas is particularly important. TG-1801 is an antibody therapy with an effector arm with CD47 blocking activity and targeting CD19. It targets the "don't eat me" signal to macrophages, promoting the consumption of tumor cells. Trials of this agent include patients with both transformed follicular lymphoma and Richter's transformation. Venetoclax, a BCL2 inhibitor, has been studied both as a single agent and in combination with chemoimmunotherapy in patients with Richter's transformation. Work from Dr. Matt Davids showed that venetoclax monotherapy had efficacy in RT, and the addition of venetoclax to R-EPOCH (VR-EPOCH) is also being studied in patients with RT and included patients with prior venetoclax and BTK inhibition as well as patients who were previously untreated. LOXO-305, a reversible BTK inhibitor, showed single agent activity in patients with RT including both patients who were naïve to BTK inhibition and those with prior BTK therapy. There were responses in 75% of a small cohort.

Interestingly, PD-1 expression has been demonstrated to be increased on large cells of patients with RT, and an ongoing study of nivolumab plus ibrutinib in RT showed a 42% overall response rate. However, these responses did not show sustained durability, but demonstrate that novel approaches may be an important avenue to pursue in this population.

Dr. Nastoupil concluded by addressing important areas for future research. Importantly, there are many combinations currently being evaluated in transformed lymphomas, but far fewer than in DLBCL. One important area that needs to be further elucidated is the clonal relationship between transformed lymphomas and the original disease, as outcomes are worse in clonally-related lymphomas versus unrelated lymphomas: it is important to characterize transformed lymphomas with tissue. ctDNA analysis by CAPP-seq also offers an interesting new area for correlation, but it remains to be seen whether we can use this for treatment selection or to risk stratify.

Another important consideration is that with the advent of new databases and data collection tools, access to more "real world" evidence in these populations is possible. The advantages of these methods are that they are more efficient, inclusive, less costly and include patients excluded from prospective studies due to exclusion criteria or comorbidities. However, there are many unmeasured confounders and biases inherent in the data as well as poor follow up and conflicts of interest.

Dr. Nastoupil also made several suggestions for minimizing barriers to drug development. Inclusivity in trial selection is key and reducing barriers to trial enrollment, including enrolling patients with CNS involvement, are important keys. More efficient study design, including moving on from "3+3" design, and novel endpoints are important. While there are many treatment options available, given the rarity of transformed lymphoma, there is a need for strong collaborations with rational and impactful study design.

Dr. Rajat Bannerji, Rutgers Cancer Institute of New Jersey, continued with a discussion of bispecific antibody therapy (BiTE) and CAR T cell therapy in transformed lymphoma. Currently, three CAR T products (lisocabtagene maraleucel, axicabtagene ciloleucel, and tisagenlecleucel) are approved for DLBCL . All three included tFL in their trials. In the ZUMA-1 trial of axi-cel, 16% of patients had tFL, but were grouped with primary mediastinal B-cell lymphoma for subgroup analysis- two-thirds of this group had tFL. The overall response rates of that combined group were similar to that of the DLBCL group with a trend towards a higher CR rate. In the TRANSCEND trial of liso-cel, 29% of patients had DLBCL transformed from indolent NHL including 5 with RT. Similarly, ORR and CR rates were slightly higher in patients with tFL than the overall population with a trend toward improved survival. tFL appears to have better outcomes than other transformed histologies.

Real world outcomes with these products have also been published, which include a higher percentage of transformed lymphomas. Despite patients with more comorbidities and allowing for bridging therapy, efficacy and safety appears to be comparable to those patients on the original trial.

Bispecific antibody therapy also offers an exciting option for these patients with odronextamab, mosunetuzumab, epcoritamab, and glofitamab all enrolled patients with transformed disease. However, no specific expansion cohorts for transformed lymphomas were included in these studies and histologic subset analyses for transformed disease have only been published or presented for glofitamab and mosunetuzumab.

Dr. Bannerji also discussed several potential biomarkers for bispecific antibody therapies. Some studies have shown that reduced immune infiltration may predict for FL patients at risk for POD24. However, with ondronextamab, tumor infiltration did not predict for response to therapy while PD-L1 was predictive of response. Tumor infiltration did not predict for outcomes in studies of glofitamab either.

Dr. Bannerji raised several questions about the future of T-cell based therapies in transformed lymphoma. One key question is how to design studies to optimize understanding of T-cell treatment in transformed lymphoma. Some suggestions included pre-specified cohorts to help determine if the trends toward higher response rates in tFL are real, and further search for more biomarkers of response. Importantly, we also suspect that the results of future trials will change the landscape of transformed lymphoma as it may make CAR T available in the second line. Other key issues include determining the role of bispecific antibody therapy in the treatment sequence and whether immunotherapies help to abrogate the negative associations of high-risk mutations.

Next, the presenters and full panel participated in a discussion of transformed disease. Panelists included Anthony Mato, MD, MSCE, Memorial Sloan Kettering Cancer Center, Andy Zelenetz, MD, PhD, Memorial Sloan Kettering Cancer Center, Pier Luigi Zinzani, MD, PhD, University of Bologna, and Tanya Siddiqi, MD, City of Hope Comprehensive Cancer Center.

The first question raised addressed barriers to enrollment on trials for transformed lymphomas. Dr. Nastoupil noted that there is a significant desire to see efficacy in early phase studies and not to kill a drug, but that we need to be more inclusive in our enrollment criteria during dose-finding so we can feel comfortable with safety in a broader population of patients. Dr. Zelenetz suggested an alternate path: rather than include sicker patients up front, be rigorous with selection initially and then include expansion cohorts. He suggested impressing upon drug companies and regulators that transformed lymphomas are an unmet need and so expansion cohorts can be included that do not contaminate the original cohort. He also pointed out the tension between broad-based approaches that include as many patients as possible versus targeted approaches. Dr. Advani agreed with the need to keep patients with transformed lymphoma separate both for pragmatic reasons of not killing the drug but also to better understand the effects of the drug in this disease. Dr. Siddiqi also noted the importance of pushing to phase II studies once a signal is seen in phase I, but that we need help from drug companies to get phase II studies with multicenter collaborations. Dr. Zinzani mentioned the lack of data for rarer histologies like transformed MZL and suggested real world data as a way to obtain it.

The next question that was raised was which investigational agents hold the most promise and why? Dr. Smith described enthusiasm for CAR-T. Dr. Mato noted that the hard part of integrating CAR-T is lack of access outside of academic centers. In terms of multi-agent regimens, most drugs are experimental and from different companies, and so a commitment was needed from drug companies and criteria need to be modified to reduce washout times. Dr. Siddiqi responded that CAR-T cells are a potentially curative option similar to transplant, which makes it more reasonable that it is only available in academic centers. Dr. Mato posited that if CAR-T therapy is to move forward to transformed disease, transformed lymphomas can no longer be a subset of larger studies. Another key point is durability, and whether patients relapse with indolent or aggressive histology. Dr. Bannerji pointed out that CAR-T is heading toward earlier lines of therapy, and if curative, we can even consider bringing it into the first line, but Dr. Smith noted that moving it up likely needs to be predicated on better safety and efficacy data. Dr. Cheson added that both mosunetuzumab and CAR-T have already been studied in the frontline setting, and patients with transformed lymphomas tend to do poorly with traditional chemoimmunotherapy, and so these T-cell directed therapies should

be moved to the front line so we can move away from chemoimmunotherapy. Dr. Bannerji noted that mosunetuzumab in frontline DLBCL in elderly patients, even patients who were not eligible for R-mini-CHOP, did well.

The panel next discussed the key correlative components of clinical trial design and planning, specifically with regards to tissue sampling. Dr. Zelenetz noted that understanding the microenvironment is extremely important for bispecific and CAR-T therapies. However, getting tissue is difficult and expensive. Dr. Thieblemont suggested imaging correlatives, such as tumor volume, SUV max, and metabolic activity may be important and are biopsy-free. Dr. Malek raised several suggestions on how to improve efficiency of biopsy collection. Dr. Nastoupil described the importance of engaging scientists early and of obtaining tissue and blood from every single study. Dr. Mato raised the question of cell-free DNA and liquid biopsies to address these issues, and Dr. Nastoupil and Dr. Zelenetz responded that it is better to have samples because cell-free DNA samples do not allow you to learn about the tumor microenvironment. Ideally it is best to have on-treatment biopsies, but these can be difficult to obtain.

Finally, the panelists discussed the utility of "real world" data and databases. Dr. Mato espoused that the quality of data is poor and degree of missing data in these databases is extensive. In Flatiron data, you cannot see PFS or even cycles, and so that makes these studies hypothesis-generating only. Ultimately you need patient-level data and correlation with tissue samples. Dr. Zelenetz raised the possibility of virtual tissue banks to pool data given how difficult it is to get tissue. Dr. Smith noted that trials have few patients with transformed lymphomas, which in turn leads to few samples, making the ability for different centers to pool samples and trial data extremely important.

Session V: Clinical Trials, Part 2

The Clinical Trials Session (Part Two) was moderated by Bruce Cheson, MD, FCAP, FAAS, FASCO and Anthony Mato, MD, MSCE, Memorial Sloan Kettering Cancer Center and featured scientists and industry experts who have conducted work in the area of transformed lymphomas, and regulatory experts. They offered their perspective on relevant issues which factor into the progress of clinical trials, including novel endpoints, trial design, accrual and the opportunity for international collaboration. Panelists included: Rob Chen, MD, AstraZeneca; Anita Gandhi, PhD, Bristol-Myers Squibb; David Hyman, MD, Loxo Oncology at Lilly; Yvette Kasamon, MD, US Food and Drug Administration; Ginna Laport, MD, Genentech; Frank Neumann, MD, Kite, a Gilead Company; Roula Qaqish, PharmD, AbbVie' Nicholas Richardson, DO, MPH, US Food and Drug Administration; Jatin Shah, MD, Karyopharm; and Ken Takeshita, MD, Daiichi Sankyo.

During the session, several challenges to studying transformed lymphomas were identified. Overall, there was a consensus that transformed lymphomas are a relatively rare disease, and the rarity can pose challenges in terms of trial accrual. There were varying viewpoints among industry representatives on whether the rare nature of the disease was a barrier or an opportunity. On the one hand, if there are few patients with the disease, the disease may be a lower priority from a development perspective. However, on the other hand, there was essentially unanimous consensus that improved therapies for transformed lymphomas represent an unmet medical need and there is an interest in studying these patients to improve outcomes. There was also a consensus that a collaborative approach that involves academia and industry is required to move the field forward.

The biologic heterogeneity of the disease also poses unique challenges. Even within subtypes of transformed lymphomas, there is a great degree of biologic and clinical heterogeneity. For example, in CLL and Richter Transformation (RT), given differences in outcomes, it is important to determine whether the underlying CLL is clonally related to the transformed disease, and there are not readily available commercial tests to do this. Disease heterogeneity can be a challenge when seeking regulatory approval. It also makes it difficult to identify a drug for study that will treat all patients under the umbrella of "transformed lymphomas." However, there are molecular

subtypes of other lymphomas that have been identified (e.g., diffuse large B cell lymphomas). Identifying biomarkers of disease to identify a biologically-related or comparatively homogenous group within the large umbrella of transformed lymphomas may be helpful in designing effective therapies.

Another challenge is that there are no specific regulatory approvals for transformed lymphomas such as RT, except for CAR-T for tFL. Without clear regulatory approvals, it is hard to know what the comparator should be during study (e.g., historical clinical trial data, subgroup analyses or real-world evidence). Furthermore, the lack of a standard of care makes it difficult for companies to see a pathway forward for regulatory approval. The "measure of success" for transformed lymphomas remains an important question. One proposed solution to the lack of a standard comparator arm and historical clinical trial data is to use synthetic controls or real-world evidence to define the benchmark against which novel therapeutic approaches may be compared. While this is a possibility moving forward, there can be issues with the quality of real-world data so the data quality must be considered.

From a regulatory perspective, the FDA representation at the meeting expressed that rarity alone is not a barrier to regulatory action, and the FDA remains committed to working with sponsors to develop safe and effective drugs for patients with transformed lymphomas. Although there are caveats with generalizations, in rare diseases, the FDA may sometimes exercise regulatory flexibility and use a single arm phase II trial to support drug approval if the treatment has both a high overall response rate and duration of response. Therefore, the FDA recognizes that the traditional paradigm of relying on randomized phase III trials for drug approvals is not always feasible in rare diseases.

The panelists agreed that several gaps in scientific knowledge must be addressed in order to develop more effective trials. Understanding how the background of prior therapies (e.g., targeted therapies versus chemoimmunotherapy) impacts the current biology and how this should impact subsequent treatment is key. There is a need to identify biomarkers that may identify more homogenous segments of patients with transformed lymphomas who may respond to monotherapies or rationale combinations of agents that target features of disease biology. There is an opportunity for collaboration between academia and industry to develop biomarker testing.

Whether or not transformed disease should be included within larger studies of DLBCL remains an unanswered question. A related question is whether all transformed lymphomas should be studied together or separated into various subtypes. There was consensus among participants that transformed lymphomas are biologically distinct from de novo DLBCL. Additionally, transformed lymphoma subtypes also have heterogeneous biology. For example, RT is distinct from de novo DLBCL as well as other transformed lymphomas such as transformed follicular lymphoma.

Several participants agreed that whether transformed patients should be included with DLBCL patients in clinical trials is largely dependent on the specific therapy being studied and whether there exists a biological rationale for that target. One way to address the challenge of disease heterogeneity would be to develop a master umbrella protocol that allows for the collection of safety data across multiple disease subtypes, but has separate phase II study arms to evaluate efficacy in different populations. This approach is also potentially appealing from an administrative perspective.

From a regulatory perspective, the FDA shared that for rare diseases two key endpoints are considered: 1) the overall response rate and 2) the durability of response. There is a need for the response rate to be adequate as well as for the responses to be durable for the drug to be considered for regulatory approval in rare diseases where randomized phase III trials are not feasible. There may be a place for synthetic controls, and these can be helpful in providing context, but there are limitations to synthetic controls and the quality of the data. Time to event endpoints such as progression free survival and overall survival are used for randomized phase III trials but should not be used for single arm phase II trials.

Many academic clinician investigators present agreed that unique response criteria for transformed lymphomas are required to address the challenge of assessing treatment outcomes for both the transformed and indolent disease components. For example, in RT patients, unique response criteria could incorporate the Lugano response criteria, iwCLL response criteria and MRD assessments. The FDA representatives noted that modified or unique response criteria would require discussion and data would need to demonstrate that the new criteria translate into clinically meaningful benefits for patients. The FDA representation also suggested that a mini-symposium with the FDA to discuss endpoints and criteria would be possible in the future.

Overall, there are unmet needs for patients receiving initial therapy for transformed lymphomas and for patients who have received prior treatment for transformed lymphoma. In RT, the outcomes for patients are universally poor for all lines of therapy (including initial treatment). Therefore, all patients with RT should be considered clinical trial candidates given the lack of a standard of care. Additionally, clinical trials for RT should not require prior RT-directed therapy as an eligibility criterion. From a regulatory perspective it is a feasible strategy to design and conduct a trial that enrolls both front-line and relapsed and/or refractory patients if there is adequate representation of both groups of patients.

Collection of data is also key to future success. For example, it is vital that clinical trial databases have a well-defined and universally agreed upon set of demographic information for these patients that are captured in data collection. Additionally, capturing data on patient outcomes after the time of progression on clinical trials is an opportunity to learn more about transformed disease. The development of a database with standardized data entry points (whether centralized or decentralized) would help further scientific knowledge regarding patients with transformed disease.

Workshop Summary and Next Steps

Bruce Cheson, MD, FCAP, FAAS, FASCO, offered closing remarks on behalf of the Workshop Co-Chairs and Steering Committee. He noted the extraordinary discussion over the course of the two-day Workshop and thanked the expert speakers and participants for their contributions to the dialogue and debate. This Workshop marked the first time such resources were dedicated to the topic of transformed lymphomas and several important themes and action items emerged from the presentations and discussion.

The rarity and heterogeneity of transformed disease is one of the greatest challenges facing the lymphoma community and can be addressed only through multi-stakeholder collaboration and the development of shared scientific resources. Additional research and consensus are needed to both make accurate diagnoses and characterize the demographics of the affected patient population. The myriad of clinical trial design issues highlighted throughout the Workshop must also be addressed, both in terms of the current regulatory framework in place and within the context of collaboration with the pharmaceutical industry. The workshop participants also underscored the critical nature of integrating science into clinical trial development and clinical care for patients. This will also foster a collaborative environment that can expedite the drug development process.

It was proposed that convening a task force as well as a mini symposium in conjunction with the FDA would be important to address these issues and impact change. It was further suggested that the LRF, with its history of convening global consortia and scientific meetings, is best poised to develop such a forum and a collaborative mechanism whereby the challenges facing the community can be addressed. LRF can also harness the interest of the lymphoma and CLL patient community, to both educate patients and ensure that the larger effort remains focused on patient-centered drug development. Immediate next steps will include the development of a Workshop proceedings paper and related submission to a peer-reviewed journal by the Workshop Steering Committee. LRF staff will work with Workshop leadership to convene a follow-up meeting to discuss the possibility of forming a Transformed Lymphomas Task Force and identification of necessary resources.

References

1. While some speakers used the term "Richter's Syndrome", there is no clear syndrome, and we prefer the term "Richter's Transformation".
2. Subset 8 refers to a biologic subset of CLL with stereotyped IgG receptors associated with more aggressive disease and a higher risk of transformation.
3. There is variability in the literature regarding the percent of patients with transformation of CLL to DLBCL versus HL. Earlier, a speaker proposed that this is 80% and 20%, respectively, whereas this speaker states 90% and 10%, respectively.

LYMPHOMA
RESEARCH • FOUNDATION

National Headquarters
Wall Street Plaza
88 Pine Street, Suite 2400
New York, NY 10005

LRF Helpline
(800) 500-9976
Helpline@lymphoma.org

lymphoma.org