CLINICAL DEVELOPMENTS IN FOLLICULAR LYMPHOMA

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The Follicular Lymphoma Foundation is a global charitable organization on a mission to find new treatments and a cure for follicular lymphoma (FL). We are committed to pushing the boundaries of research, delivering real impact for FL patients and beyond. To learn more please visit https://www.theflf.org/.

FOREWORD

Follicular Lymphoma Foundation's (FLF) mission is to lead new and determined efforts to find innovative treatments and cures for follicular lymphoma (FL).

We have a dedicated scientific program that aims to make curative therapies available to FL patients as soon as possible. It is our absolute priority to drive transformational change in scientific research, in order to deliver the greatest benefits and impact to FL patients. Therefore, it is vital that this research is focused on the latest areas of FL therapeutic development.

This paper provides a review of the current landscape in FL, as part of our work to validate our scientific priorities and maintain our focus on the most important research goals. We are delighted to share this paper with you and hope that clinicians and scientific researchers will find it insightful and a valuable source of reference to understand the current landscape of follicular lymphoma better.

At the FLF, we place the patient at the heart of what we do, and when choosing our scientific projects, priorities, and strategic partnerships, we are single-mindedly focused on maximizing impact for FL patients. We strive for therapies with the potential to achieve a cure at first relapse and to fast-track their path to clinical application.

Through our Targeted Accelerated Research program, which includes our CURE FL Awards, we aim to allocate significant funding toward the most promising scientific directions. By encouraging and promoting the development of a cure at first relapse, we seek to substantially lessen the toll of this disease. Alongside CURE FL Awards, our Centres of Excellence program will foster strategic partnerships with leading academic institutions to propel knowledge and treatment advancements for FL through transformational approaches.

We have worked in partnership with our strategic advisors at the Milken Institute to produce this comprehensive report and are extremely grateful for their support.

Founding the FLF has been an incredible honor and privilege. I am immensely proud to witness its growth and impact in the fight against FL.

Nicola Mendelsohn, CBE

Founder and Chair

Follicular Lymphoma Foundation

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EXECUTIVE SUMMARY

Follicular lymphoma (FL) is an indolent non-Hodgkin lymphoma (NHL) currently considered incurable. Because of the heterogeneity of the disease, assignment of treatment at diagnosis can be challenging, and the course of the disease varies significantly from patient to patient. Nearly all patients experience relapse, and many experience multiple relapses over the course of their disease. The impact of several courses of treatment and the devastating realization that no cure for FL currently exists can take a significant toll on the physical and psychological well-being of patients.

The Follicular Lymphoma Foundation (FLF) has engaged MI Philanthropy to perform an assessment of the therapeutic landscape to inform future initiatives, and the insights are shared here. FLF seeks to substantially lessen the toll on patients by encouraging and promoting development of a cure at first relapse, in particular through the FLF **CURE FL Awards**—**CU**rative **R**esearch to **E**liminate **F**ollicular **L**ymphoma. The learnings shared in this document promote an understanding of the landscape that will drive research priorities in 2023.

FL is a heterogeneous and currently incurable disease; therefore, treatment options for FL are numerous but not standardized and include chemotherapy agents, steroids, and monoclonal antibodies. Patients remain underserved, treatment options are complex, and patients may experience multiple relapses, resulting in extended periods of uncertainty between treatment phases. Approvals for FL therapy have accelerated in the past decade, including a new anti-CD20, lenalidomide, PI3K inhibitors (most now withdrawn), an epigenetic targeted drug that inhibits EZH2, and most recently, chimeric antigen receptor (CAR) T and bispecific antibody treatments. It is too early to determine whether a fraction of patients may be cured with these novel treatments, and it is already clear that none of those results in a cure for the majority of patients treated—indicating a continuing and compelling need for new therapeutic options.

Exploration of the clinical trial landscape for FL reveals several early-phase clinical trials, indicating innovations in the field, but the early stage of these trials indicates that it will take several years for successful therapies to progress through clinical trials, approval, and commercialization. Most of the current clinical trials for FL are assessing therapies that harness the immune system in various ways—including engineered cell therapy, antibody-based approaches especially bispecific T cell engagers, and vaccines.

Improvements may come from processing and design optimization that make these agents more effective or easier to produce, and therefore more accessible, and/or less toxic. Interest in epigenetic therapies remains high, based on the commonality of epigenetic mutations in FL and the success of tazemetostat, although epigenetic drug development reaching the clinic has lagged. In addition, other novel targets are under assessment.

The following key findings from the research presented in this report reveal promising innovations in the field, as well as limitations that will need to be addressed in order to accelerate successful therapeutic development.

- **Innovative immunotherapeutic modalities**, including cancer vaccines, cell therapies, and bispecific antibodies, are moving into clinical trials with increasing frequency. Remaining challenges of immunotherapies include identifying those patients most likely to respond, optimal timing for administration of these therapies, mechanisms of resistance, and rationally designed combination therapies that result in synergistic and durable responses.
- **Novel drivers and pathways** are seeing an exciting expansion in early-phase clinical research in follicular lymphoma. Patient identification and stratification for clinical trials assessing these therapeutics could greatly improve therapeutic success and outcomes, and rational combination therapy determination could create lasting responses and decrease recurrence.
- **Accelerated movement** of therapies out of the lab and into clinical trials can be bolstered by the development and incorporation of biomarkers into clinical trial design as they better define the target patient population and enhance the biological understanding of targets and how they are impacted by the therapeutic, which may improve knowledge of how tumor-immune interactions influence the efficacy of immunotherapies.

INTRODUCTION

Follicular lymphoma is a type of slow-growing non-Hodgkin's lymphoma. FL diagnosis and treatment decisions on timing and treatment selection can be challenging. Many patients are held in a "watch and wait" pattern—otherwise known as "active surveillance," or from a patient perspective "wait-and-worry"—during which patients are monitored but no treatment is given.

This report is focused on current and emerging follicular lymphoma therapeutics, highlighting current therapeutics and treatments by modality, phase of development, and molecular mechanism of action. The information highlighted supports efforts of the FLF to drive research into better treatments and find the fastest pathway to a cure. Importantly, this document demonstrates that although drug development for FL has been burgeoning in the past five years, key areas should be addressed to accelerate the path to a cure:

1. overcoming barriers to the identification of novel targets for effective drug development;
2. enhancing the understanding of how the tumor microenvironment impacts malignancy; and
3. focusing on the relative paucity of mechanisms to improve clinical trials given the long time-course of FL and lack of interim endpoints, as well as for stratifying patients for more effective targeting of treatments.

Some of the most significant challenges associated with FL diagnosis and treatment include the following:

- The clinical course of FL is heterogeneous; some patients are safely observed over several years without requiring treatment, while other patients may experience rapid disease progression. Some patients require multiple lines of treatment that can lead to decreased quality of life.
- Nearly all patients experience relapse, and many experience multiple relapses over the course of their disease.

- In the 20 percent of patients that progress within two years post-treatment (POD24), five-year survival rates are as low as 50 percent (Leonard 2022).
- Assignment of appropriate treatment at diagnosis faces significant challenges. Additionally, an increased understanding of how newly developed drugs can be most effectively applied during clinical trials is necessary to increase the potential for drug approval and ensure that patients are assigned the most appropriate treatment for their specific disease.

It is encouraging that outcomes for patients with FL have improved substantially during the past 40 years: The five-year survival rate has increased from 65 percent in 1980 to 90 percent in 2022 (National Cancer Institute 2022). Although first-in-class therapies have recently been marketed for FL, the 1997 introduction of the anti-CD20 monoclonal antibody rituximab remains the defining advance in the field. Progress will accelerate with an enhanced understanding of the biology of the disease within its microenvironment and dedicated application of a promising therapy to a more challenging subtype of lymphoma—one that is rare, indolent, and heterogeneous, and has a high propensity to relapse.

However, despite this fact, and the fact that the five-year survival rates are now reaching 90 percent, an urgent need for effective treatments for many patients remains. This need is particularly strong for relapsed/refractory and transformed FL, specifically for those patients who progress within two years of first-line treatment. Even patients with more favorable survival rates continue with significant unmet needs, enduring increasing toxicities from therapies designated for later relapses. This gap emphasizes the necessity for safer therapies, and the importance of quality-of-life assessment and shared decision-making.

FLF has a laser focus on driving therapeutic development. To support that aim, this report explores the landscape of US Food and Drug Administration (FDA)-regulated drugs and biologics in addition to therapies in clinical trials as of late 2022. This assessment of current therapeutics is based on data from clinicaltrials.gov (see Appendix for overview of clinical trial search methodology) alongside academic peer-reviewed papers. Further, interviews with experts in the field, in addition to presentations and discussions that occurred during the 64th Annual American Society of Hematology Meeting and Exposition in December 2022, highlighted research and resource needs that serve as opportunities for research acceleration. A thorough review of publications and abstracts for recent scientific insight was defined for the period between September 2021 and August 2022. Where prior research was informative or provided background information on the disease, treatment strategies, or historical knowledge, those works are referenced as well.

THE STATE OF FOLLICULAR LYMPHOMA TREATMENT

The current standard state of FL treatment is described first below, followed by review of more recently approved and novel treatment options.

Initial management of FL depends on disease progression at the time of diagnosis. Because of its indolent nature, mild symptoms, and B cell movement through the circulatory system, the majority of patients diagnosed with FL present with widespread disease. Nonetheless, even in patients with stage III or IV disease, if there are no clinical symptoms and a low tumor burden, the patient is monitored but treatment is not initiated. Comparing this strategy to either early rituximab monotherapy or rituximab plus chemotherapy, overall survival does not differ (Nastoupil et al. 2016). As such, the "watch and wait" strategy remains the recommended approach to postpone treatment-related side effects and late effects, which may not appear for months or years post-treatment.

The timing and selection of first-line therapy for FL depends on clinical symptoms, clinical course, and tumor burden. A subset of patients with well-localized disease can be successfully treated with radiation therapy and achieve long-term durable remission. Four large prospective randomized clinical trials support treatment with a combination of rituximab plus chemotherapy (Hiddemann et al. 2005; Herold et al. 2007; Marcus et al. 2008; Salles et al. 2008). In each case, adding rituximab improved outcomes and/or disease control, regardless of the chemotherapeutic regimen (e.g., cyclophosphamide, doxorubicin, vincristine, and prednisolone [CHOP], cyclophosphamide, vincristine, and prednisone [CVP], cyclophosphamide, adriamycin, etoposide, and prednisolone plus interferon-alpha2a [CHVP+I], or mitoxantrone, cyclophosphamide, prednisone [MCP]). Although several chemotherapy options exist, commonly used front-line regimens include bendamustine plus rituximab and rituximab in combination with CHOP (Marcus et al. 2008). Bendamustine plus rituximab is generally favored based on results of the StiL and BRIGHT clinical trials (Rummel et al. 2013; Flinn et al. 2014). Upon complete or partial remission, first-line treatment has often been followed by maintenance treatment for two years (Bachy et al. 2019), generally an anti-CD20 antibody, either rituximab or obinutuzumab, to prolong remission. Because this treatment does not confer an overall survival benefit (Cartron and Trotman 2022), maintenance has been reconsidered in the COVID-19 era because it prolongs immunosuppression, particularly antibody response to infection or vaccination.

Advanced-stage FL is currently incurable, and recurrences can be regular, though unpredictable. These recurrences must be monitored for transformation to an aggressive histology and clinical behavior. Several questions should be considered when selecting treatment for recurrent FL:

- What was the type of previous therapy, and what was the response to that therapy?
- What was the time to recurrence?
- What are the clinical symptoms associated with the recurrence?
- How old is the patient, and do they have any comorbidities?

Treatment options can range from repeat chemo-immunotherapy to high-dose therapy followed by autologous stem cell transplantation to incorporation of targeted or alternate immunotherapies. The benefits of chemotherapy-free therapeutic options, including new antibody-based therapies, small molecule inhibitors, and immune-directed agents, are decreased toxicity and increased specificity because they are developed to specifically target malignant cells. Recently, therapeutic options for patients with relapsed/refractory FL have experienced significant advancement, and more are emerging (Matasar et al. 2019; Gordon, Smith, and Nastoupil 2023). The aim is for novel, targeted therapies and immunotherapies to support the achievement of complete remission and delay or halt progression.

Medicines for Follicular Lymphoma

Current and Future Treatment Options for Follicular Lymphoma

Key takeaways: Currently, 10 therapeutics are approved and utilized regularly for treatment of FL. These treatment options either impact the immune response to FL or target pathways that are commonly altered drivers of FL malignancy. Four therapies have been approved by the FDA and the EMA in the past five years, and FL is still considered incurable using standard therapies, indicating a need for new therapeutic options.

Current market medicines in the US are approved by FDA and in Europe by the European Medicines Agency (EMA) and made available through prescription or administration in a clinical setting. Nine products are currently approved in the US and Europe, and a tenth is available via marketing authorization to treat FL in the EU, UK, Canada, Australia, New Zealand, and Switzerland (Table 1). Therapeutic modalities of these drugs include antibodies, CAR T cell therapies, immunomodulators, targeted small molecule inhibitors, and, most recently, bispecific antibodies.

Table 1: Current Non-chemotherapy Market Drugs Approved for Individuals with FL

Therapeutic Modality	Generic Name	Approval Year	Mechanism of Action	Follicular Lymphoma Indication(s)
Antibody	Rituximab	1997 (FDA) 1998 (EMA)	Anti-CD20 monoclonal antibody	• relapsed or refractory follicular, CD20-positive B cell NHL as a single agent • previously untreated follicular, CD20-positive, B cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy
	Obinutuzumab	2013 (FDA) 2014 (EMA)	Anti-CD20 monoclonal antibody	• FL relapsed or refractory to a rituximab-containing regimen, bendamustine followed by obinutuzumab • previously untreated stage II bulky, III or IV FL, chemotherapy followed by obinutuzumab
	Mosunetuzumab-axgb	2022 (FDA and EMA)	CD20xCD3 T cell engaging bispecific antibody	• adults with relapsed or refractory (R/R) FL after two or more lines of systemic therapy
CAR T Cell Therapy	Axicabtagene ciloleucel	2015 (EMA) 2017 (FDA)	CD19 CAR T cell therapy	• relapsed or refractory large B cell lymphoma, including diffuse large B cell lymphoma (DLBCL) arising from FL, after two or more lines of systemic therapy
	Tisagenlecleucel	2021 (EMA) 2022 (FDA)	CD19 CAR T cell therapy	• relapsed or refractory FL after two or more lines of therapy
Nonspecific Immunomodulating Agent	Lenalidomide	2019 (FDA) 2020 (EMA)	Analog of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties	• previously treated FL, in combination with a rituximab product
	Interferon alpha-2b	1986 (FDA) 2000 (EMA)	Recombinant interferon; induces pleiotropic biologic responses, including antiviral, antiproliferative, and immunomodulatory effects	• FL
Targeted Therapy	Tazemetostat	2018 (EMA) 2020 (FDA)	EZH2 inhibitor	• R/R FL in patients whose tumors are positive for an EZH2 mutation and who have received at least two prior systemic therapies • R/R FL in patients who have no satisfactory alternative treatment options
	Idelalisib	2014 (marketing authorization in EU, UK, Canada, Australia, New Zealand, and Switzerland)	PI3K-delta inhibitor	• FL
	Copanlisib	2017 (FDA)	PI3K-alpha and delta dual inhibitor	• relapsed FL after at least two prior systemic therapies

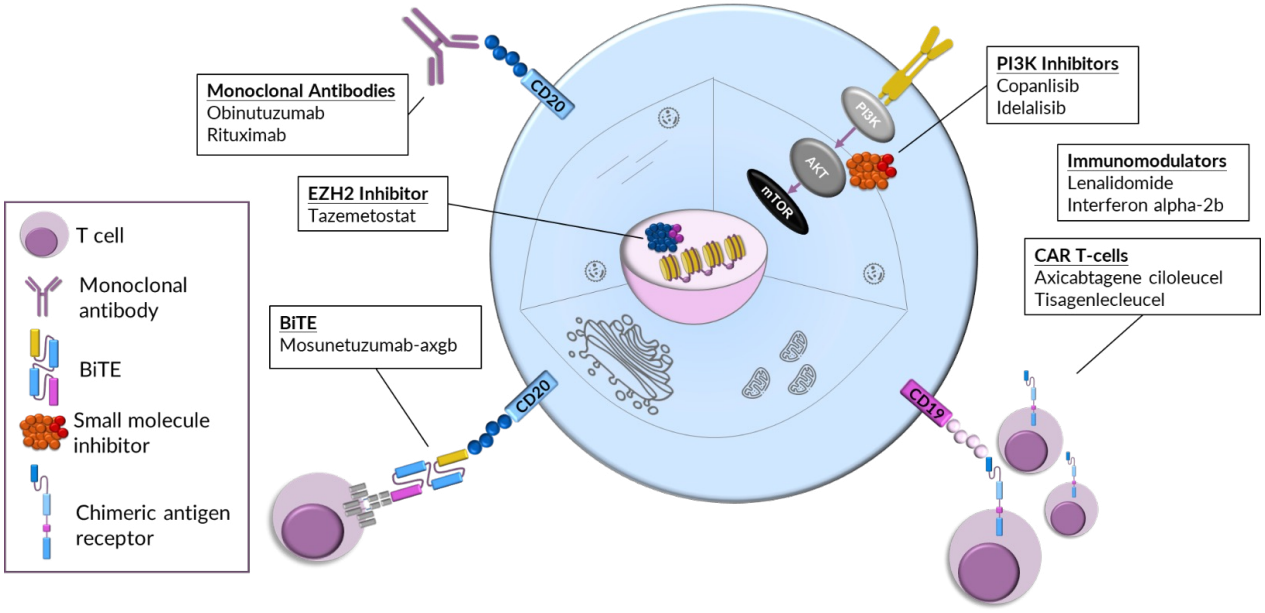
Source: Milken Institute analysis of data from National Cancer Institute (2023) and European Medicines Agency (2023)

The majority of FL therapies have been developed based on an understanding of either normal B cell counterparts of FL or the actual pathogenesis of FL. A translocation of the 14th and 18th chromosomes [t(14;18)] results in overexpression of the anti-apoptotic protein BCL2, but this translocation can be detected in some healthy individuals, pointing to the necessity of multiple hits. Researchers hypothesize that constitutive B cell receptor signaling and activation of downstream pathways, including phosphatidylinositol 3-kinase (PI3K) and Bruton's tyrosine kinase (BTK), are critical players in malignancy, resulting in drug development focused on these pathways. Moreover, mutations in the histone H3 lysine 27 (H3K27) methyltransferase EZH2 occur early and frequently in FL (Bödör et al. 2013), validating its potential as a therapeutic target. Researchers are increasingly appreciating the role that nonmalignant immune cells may also play in FL survival. Studies exploring these relationships are becoming more common and highlight additional areas of need, especially models and patient-derived tumor samples, for the research community.

Approved Follicular Lymphoma Drugs

Approved FL therapies fall into one of four modalities: antibodies, immunomodulatory agents, CAR T cell therapies, and targeted small-molecule inhibitors (Figure 1). CD19 and CD20 are the primary targets for antibody and CAR immunotherapies (less commonly CD22 and CD79b), and small molecule inhibitors target PI3K isoforms and the epigenetic regulator EZH2.

Figure 1: Modalities of Current Market-Regulated Therapeutics, Including Monoclonal Antibodies, Immunomodulatory Agents, CAR T Cell Therapies, and Targeted Small Molecule Inhibitors



Source: Modified from Pytlik (2020)

Immunotherapy

FL is a lymphoma subtype that is highly sensitive to **immunotherapy-based treatment strategies** as exemplified by the efficacy of the anti-CD20 antibody when administered as a single agent and in combination as a first-line treatment and at relapse. FL arises from the B cell lineage and typically expresses pan-B-lymphocyte differentiation antigens such as CD19, CD20, CD22, and CD79, markers that provide useful immunotherapy targets for both antibody- and cell-based therapies like CAR T cell therapy. Notably, currently approved CAR T cell therapies axicabtagene ciloleucel and tisagenlecleucel target CD19, and antibody therapies rituximab and obinutuzumab target CD20. Recently, the first bispecific T cell engager (BiTE) was approved for follicular lymphoma; mosunetuzumab-axbg binds CD20 and CD3 to engage T cells. Both CAR T cells and BiTEs direct the antitumor immune response to specific markers on the malignant cells.

Nonspecific **immunomodulating agents** either stimulate or suppress the immune system in a more general way than specific agents—such as monoclonal antibodies and vaccines—that impact the immune system through the mediation of a well-defined target or set of targets. The two FDA-approved immunomodulatory agents are lenalidomide and interferon alpha-2b, both of which impact a range of immune activities. Lenalidomide binds cereblon, resulting in the degradation of factors including Ikaros, but how these activities impact both FL directly and the tumor microenvironment remains unclear. In cell and animal models, effects on both tumor immunity and direct cytotoxicity have been identified. Lenalidomide alters a range of immune system components by changing cytokine production, regulating T cell stimulation, and enhancing natural killer cell activity (Kotla et al. 2009). Interferon alpha-2b is a cytokine that has been shown to activate anticancer immune cells, including T cells and natural killer cells, and induce the production of other cytokines (Asmana Ningrum 2014). Although interferon alpha-2b was approved for FL in 1986, nonspecific effects, toxicity, and inability to predict who will benefit have limited its use.

A challenge of immunotherapies is identifying the patients who are most likely to respond and the optimal timing for administration of these therapies. Current clinical trials continue to assess these variables in addition to optimal therapy combinations.

Targeted Therapy

Two **targeted small molecule inhibitors** have been approved for use in FL in the US and a third authorized for administration in the EU, UK, Canada, Australia, New Zealand, and Switzerland. Two of these drugs, idelalisib and copanlisib, target one or more isoforms of PI3K. The four isoforms of PI3K are PI3Kα, -β, -δ, and -γ. Despite similar structure and function, research has revealed different mechanisms of activation

and tissue localization for the isoforms, suggesting distinct roles for each (Thorpe, Yuzugullu, and Zhao 2015). The utility of Pan-PI3K inhibitors, especially those that target all PI3K isoforms, is limited because of toxicities (Chia et al. 2015). Copanlisib is an intravenous, potent, selective, and reversible PI3K inhibitor with predominant activity against the PI3Kα and PI3Kδ isoforms (Liu et al. 2013). It has been shown to induce malignant cell death and inhibit growth of malignant B cells, but its PI3Kα targeting confers unique toxicities. Idelalisib is an oral and specific inhibitor of the PI3Kδ isoform that alters pathway activation downstream of the B cell receptor in malignant B cells (Fruman and Cantley 2014; Yang et al. 2015).

Notably, as reflected in Table 1, idelalisib was voluntarily withdrawn in the US in 2022 for relapsed follicular B cell non-Hodgkin lymphoma and is only available for FL in the EU, UK, Canada, Australia, New Zealand, and Switzerland by marketing authorization. Likewise, the PI3K-delta and gamma dual inhibitor duvelisib for FL was withdrawn in the US in April 2022. As a condition of accelerated approval, applicants are required to conduct post-marketing trials to verify clinical benefit. In both cases, enrollment in confirmatory studies in FL was challenging, and the drugs were withdrawn for this disease indication. These withdrawals indicate clinical trial challenges that will be discussed in subsequent sections of this report. Finally, the PI3K-delta and casein kinase CK1-epsilon dual inhibitor umbralisib was withdrawn due to safety concerns in June 2022. Updated findings from the UNITY-CLL clinical trial demonstrated an increased risk of death in patients receiving umbralisib. As a result, FDA determined the risks of this treatment outweigh its benefits (Luttwak, Smith, and Zelenetz 2023; US Food and Drug Administration 2022).

The EZH2 inhibitor tazemetostat is also approved for FL. Epigenetic alterations are major drivers of FL, and these alterations are frequently caused by mutations in or upregulation of EZH2. When EZH2 is overactive or overproduced, B cells proliferate at an increased rate, and they are prevented from exiting the germinal center, favoring malignancy (Julia and Salles 2021). Additional studies are required to determine whether and what combination therapies might further improve outcomes and reduce resistance, especially PI3K inhibitor-acquired resistance. EZH2 tolerability makes it an attractive agent for such combination trials, a number of which are in progress, including HDAC inhibitors, with others demonstrating promise in other cancers (Li et al. 2021).

Current Follicular Lymphoma Clinical Trials

Key takeaways: The clinical trial landscape for FL is defined by early-phase clinical trials, indicating innovations in the field, but additional time will be required for the small percentage of these therapies that progress through clinical trials to be approved and marketed. The majority of clinical trials for FL are assessing immunotherapies, either as single agents or in combination with other immunotherapies or chemotherapeutic regimens, and novel strategies such as vaccines and cell therapies are increasingly entering early-phase clinical trials. In addition to novel targets that are under assessment, the potential for expansion of the therapeutic toolbox for FL is significant, but it will take several years.

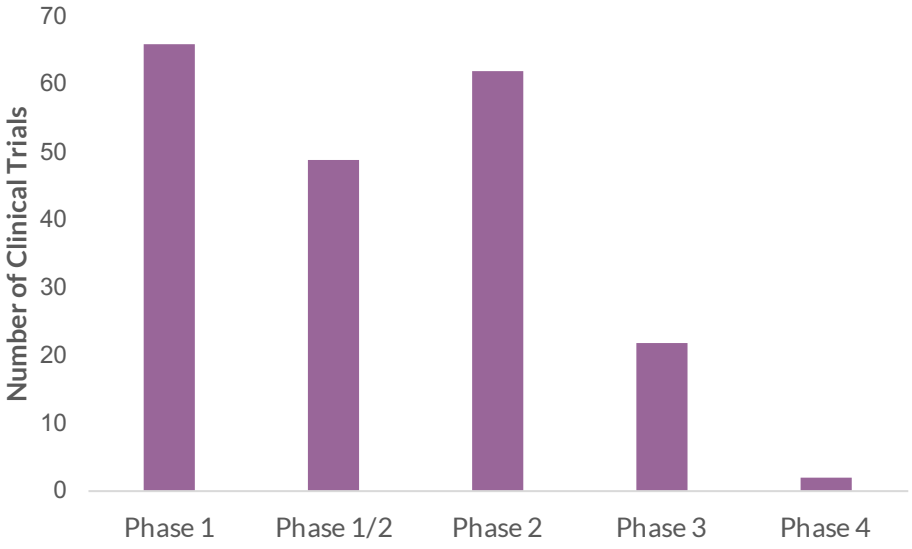
Clinical trials (see Appendix for detailed overview) are pivotal experimental assessments performed in human patients prior to a therapy moving into the marketplace. Early-phase clinical trials, Phases 1 and 2, assess early safety and efficacy signals, and promising agents or combinations are then investigated in larger Phase 3 trials, where effectiveness is confirmed, side effects are monitored, and the therapy is assessed for its ability to perform better than standard of care, potentially leading to regulatory approval. Further monitoring post-approval affirms long-term risks and benefits. FLF aims to drive therapies into early-phase clinical trials, accelerating the movement of novel treatment options out of the lab and into patients, and de-risking them to increase attractiveness to industry.

Follicular Lymphoma Drugs in Clinical Trials

As of September 2022, 201 interventional clinical trials in which FL patients are eligible for enrollment were listed in clinicaltrials.gov. Notably, these trials could also enroll patients with other hematologic malignancies, but FL was an eligibility criterion for all trials assessed. The drug development pipeline in which patients with FL are eligible for

enrollment is robust with a predominance of early-phase clinical trials (Figure 2), which is a promising figure considering the limited number of approved therapies and the recent withdrawal of several targeted therapies. The majority of early-phase clinical trials do not progress to later phases and could take several years to reach approval if they do, so it is important to strategically identify the most promising therapeutics for well-defined patient populations to accelerate successful therapeutics through the pipeline.

Figure 2: Follicular Lymphoma Clinical Trials by Development Phase

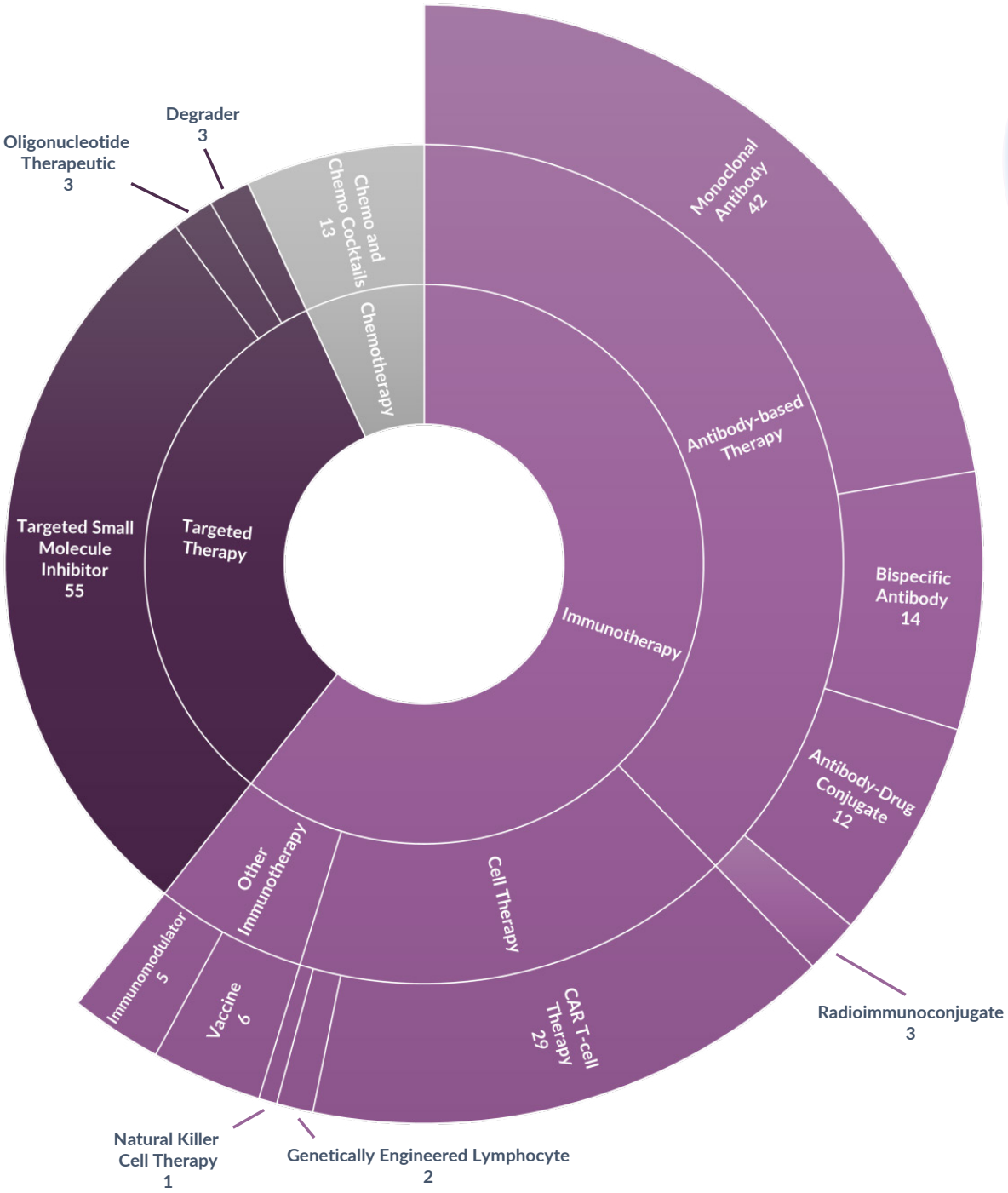


Note: These trials include duplicate compounds that may be used in different combinations or over different treatment courses.

Source: Milken Institute analysis of clinicaltrials.gov (2022)

Notably, clinical trials for FL represent an exciting expansion of drug mechanisms and targets. These include novel, non-CAR-based cell therapies, vaccines, bispecific antibodies, antibody-drug and antibody-radiotherapy conjugates, degraders, and oligonucleotide therapies, in addition to a variety of novel combinations of approved therapies (Figure 3).

Figure 3: Modalities of Current Therapies in Clinical Trial



Note: These numbers compile all clinical trials regardless of whether replicate assets are assessed. Immunotherapies are the predominant therapeutic modality in clinical trials for FL.

Source: Milken Institute analysis of clinicaltrials.gov (2022)

Increased understanding of FL drivers as well as findings in other lymphomas have greatly expanded the options for FL therapeutic targets. Moreover, the promise of immunotherapies has spurred integration of novel immunotherapy modalities into FL clinical research. The range of targeted and immunotherapy targets has expanded significantly in recent years, as indicated by the preponderance of novel targets in clinical trials (**Figure A**). This expansion of potential targets exemplifies the important impact of the genomic and microenvironmental understanding of FL on drug development.

Immunotherapy

Chimeric antigen receptor (CAR) T cell therapy is the predominant cell therapy in clinical trials for FL. CAR T cell therapy uses the patient's own immune cells to fight cancer. CAR T cells are cells that are genetically altered in a lab to express targeting molecules that allow them to locate and destroy cancer cells more effectively. With the success of CD19 targeting CARs axicabtagene, ciloleucel, and tisagenlecleucel, several new CAR T cells in clinical trials also target CD19. In addition to CD19, CAR targets under investigation in clinical trials include CD22, CD28, CD20, and CD5. CAR T targeting two antigens, for example CD19 and CD22, are in trials to determine whether they may be more effective, possibly killing cells that do not express high levels of one of the targets. CAR T cells that are engineered to also secrete local cytokines may be a way to amplify the killing effect. CAR T cells, as other T cells, can also become "exhausted" (nonfunctional) or be suppressed by the microenvironment. Studies are underway to reduce or overcome these issues.

A well-recognized challenge of CAR T cell therapy is the potential, but often manageable, toxicity caused by cytokine release syndrome. This systemic inflammatory response is caused by cytokines released by infused CAR T cells, which can lead to organ dysfunction. There are also neurologic toxicities that are not as well understood. Advances are being made in predicting risk of toxicity, early interventions to minimize toxicity, and engineering the CAR T cells to reduce toxicity. Another limitation of CAR T cells is that it takes weeks to produce them. Several new rapid production methods are being explored to address this problem, including, but not limited to, the use of lentiviral vectors to transduce nonactivated T cells, automated artificial intelligence-driven CAR T cell manufacturing platforms, and automated transposon-based manufacturing. Nonetheless, although CAR T cell therapy can be effective in FL, cost, toxicity, and technical complexity of current generation cells are limiting their use after other treatment options have failed. CAR T cells are generally administered to patients who are heavily pretreated or specifically after two or more prior lines of systemic therapy (axi-cel and tisa-cel). Efficacy as even a second-line therapy has not been sufficiently assessed (Mohty and Kharfan-Dabaja 2022). When these limitations can be overcome, there is hope that CAR T cells will be implemented as earlier lines of therapy.

CAR T currently are individualized autologous products. Approaches are being taken to make an allogeneic "off-the-shelf" CAR T product, requiring engineering to avoid GVHD, which would avoid treatment delays and cost, making such a product available to a wider range of patients. CAR T cells contain the target and some components of the T cell killing signals on one molecule, bypassing the normal T cell receptor (TCR). However, the CAR T cell killing signals are weaker than endogenous TCR signaling. Researchers are exploring alternative methods for engineering patient T cells to identify and kill cancer cells more effectively. One way is to engineer the TCR, reprogramming T cells to target tumor antigen in a nonmajor histocompatibility complex (MHC)-restricted fashion, to harness the full spectrum of T cell receptor signaling, hypothesizing that the engineered T cells yield more efficient signaling upon binding of the T cell to the tumor antigen (Horton et al. 2019). Current clinical assessment of this cell therapy is in the early phase (1/2) so it is not yet clear whether this T cell therapy will be more safe or effective than CAR T cell therapy.

Natural killer (NK) cells are immune cells with the capability to kill cancer cells by direct recognition of proteins on the cancer cell surface. NK cell therapy in cancer offers specific theoretic advantages compared to other cell therapy options. Importantly, there is significant cost and time savings because they are available "off-the-shelf," that is, not required to be from or matched to the patient, whereas CAR T cells and other genetically modified immune cells require time-intensive processing prior to use. NK cell biology is not as well understood as T cell biology, and various protocols to make and expand NK cells have been proposed. A single Phase 1/2 clinical trial is assessing NK cell therapy in patients with relapsed or refractory multiple myeloma or relapsed/refractory CD20-positive non-Hodgkin lymphoma (including FL). These NK cells are expanded under the influence of nicotinamide, which is hypothesized to improve their cancer-killing ability and improve their ability to home into tumor cells. Interleukin-2 is administered after the NK cells with the goal to further boost the immune response to the NK cells. This trial is first-in-human, indicating the novelty of this therapeutic strategy.

Cancer vaccines are a form of immunotherapy that trains the immune system to better identify a cancer cell so that it can better recognize and eliminate it, as a vaccine does with a virus. Three cancer treatment vaccines have been approved by FDA, indicated for bladder cancer, prostate cancer, and melanoma. Often, cancer cells have certain molecules (antigens) on their surface that differentiate them from healthy cells. A vaccine introduces these molecules into the patient, and the immune system is boosted to identify them and destroy the cancer cells on which the antigens are expressed. Six current vaccine clinical trials include patients with FL. In addition to personalized vaccines that target the proteins expressed in an individual's cancer (Neo Vax, GVax, and Oncoquest-L Vaccine), vaccines currently in clinical trials target a range of antigens, including CD20, CD22, CD37, and CD268. All six vaccines are in early-phase clinical

trials (50 percent Phase 1, 33 percent Phase 2, and 17 percent Phase 1/2), indicating the novelty of this modality in FL. Vaccines are also being included within cocktails with immunotherapies—including CAR T cells and monoclonal antibodies—to boost the immune system against the cancer and infections that might arise in the setting of altered immune activity. Identifying the more effective combination therapy options will be an important next step in moving vaccines forward in FL. Moreover, identification of the most appropriate antigens for immune cell activation via vaccine will be required to advance the most promising vaccines.

Immunomodulating agents, described previously in this report, alter the activity of the immune system. Five current clinical trials integrate nonspecific immunomodulatory agents for FL treatment. The majority of agents block the immune checkpoint PD-1, or the protein that binds to it, PD-1L. PD-1 is a protein expressed on T cells that restrains the cell-killing properties of T cells. Agents that block PD-1 or PD-L1 activity release the restrictions on the T cells and enhance their ability to kill cancer cells. Some of these agents are effective against some lymphomas but have not seemed as effective against FL (Armand et al. 2021). Another immunomodulator in clinical testing blocks the myeloid checkpoint CD47. As PD-1 does with T cells, CD47 halts the cell-killing activity of another immune cell type, macrophages. When CD47 is blocked, the immune response against cancer is enhanced. Preliminary trials of CD47 blocking agents have been somewhat problematic, although further investigations are ongoing (Bouwstra et al. 2022).

The triumph of the anti-CD20 monoclonal antibody rituximab has paved the way for the development of **antibody-mediated therapies** targeting a variety of FL markers. Antibodies can directly target tumor cells while promoting the induction of long-lasting antitumor immune responses. When considering the **monoclonal antibody** landscape for all cancers, more than 80 have been FDA approved. Notably, these 80 antibodies only target approximately 50 targets (Ecker, Jones, and Levine 2015). Of these, five antigens—tumor necrosis factor-alpha [TNFα], CD20, epidermal growth factor receptor, human epidermal growth factor, and vascular endothelial growth factor alpha—feature as targets for as many as 23 different antibodies (Martineau et al. 2019). The utilization of so few targets across many antibody treatments indicates that the identification of new and effective targets is a primary challenge for antibody therapy development. In FL, 42 clinical trials are assessing monoclonal antibody therapies, either as single agents or in combination, the majority of which target CD20. Other monoclonal antibody targets in clinical testing include CD40, OX40, ICOS, CD19, and CD37.

Ten of the 14 clinical trials assessing **bispecific antibodies** are testing the CD20 x CD3 T cell-engaging bispecific antibodies (mosunetuzumab and epcoritamab) in novel combinations with other immunotherapies, including CAR T cells and monoclonal

antibodies. These bispecifics redirect T cells to eliminate malignant B cells by binding CD20 in cancer B cells and CD3 on T cells, bringing the cytotoxic activity of the T cells to the cancer cells. Other bispecifics perform similar functions by replacing the CD20 targeting with CD19. A unique bispecific, TG-1801, targets the B cell marker CD19 in addition to the signal used by tumor cells to evade macrophage-mediated cell "eating" (phagocytosis), mediated by CD47 (Hawkes et al. 2023). By blocking CD47, the bispecific antibody is theorized to re-expose the lymphoma cells to be phagocytosed by macrophages. As bispecifics demonstrate increased success in FL, it will be important to optimize selection of targets on both the T cell and cancer cell. It will also be critical to determine how combinations with other immunotherapies can further improve efficacy.

Antibody-drug conjugates (ADCs) deliver chemotherapy agents directly to the cancer cells by using targeting antibodies. They do so by attaching antibodies that bind to specific targets on the cancer cell to chemotherapeutic agents through a linker. After the antibody binds to the cancer target that is internalized upon binding, the ADC releases the cytotoxic chemotherapy inside the cancer cell, reducing the off-target effects typical of systemic administration. ADCs currently in clinical testing include an assortment of cancer cell-targeting antibodies and chemotherapeutic agents (**Table A**).

Radioimmunoconjugates are made by attaching a radioactive molecule to an immune substance. In the case of radioimmunoconjugates used for FL therapy, the immune substance is a monoclonal antibody (**Table A**). As with ADCs, the antibody (Ab) directs the radioactive therapy to the cancer cell, resulting in radiotherapy treatment that occurs specifically at the cancer site, reducing less-specific radiotherapy delivery to normal tumor-adjacent cells. Notably, Y90-ibritumomab tiuxetan is a radioactive anti-CD20 Ab approved for previously untreated follicular non-Hodgkin's Lymphoma (NHL), which achieves a partial or complete response to first-line chemotherapy, but this radioimmunoconjugate is rarely prescribed therapy.

Targeted Therapy

The clinical trial pipeline reveals a range of potential targets for FL therapy. Notable targets of interest include, but are not limited to, the following:

- B cell lymphoma 2 (BCL-2): Cell death regulating protein and associated BCL-2 family members
- Ikaros/Aiolos: Hematopoietic-specific transcription factors involved in the regulation of lymphocyte development
- DNA methyltransferase: Epigenetic regulator
- Nuclear factor erythroid 2–related factor 2 (NRF2): Oxidant stress regulator
- Homologous recombination: DNA damage response

- Histone deacetylase: Epigenetic regulator
- Proteosome: Protein degradation
- Exportin 1 (XPO1): Nuclear export
- Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1): NF-kappa-B pathway activator
- Cyclin-dependent kinase 9 (CDK9): Cell cycle regulator

These additional targets indicate that basic and translational research is revealing more about the drivers of FL malignancy, but the preponderance of therapies that address similar targets, such as Bruton's tyrosine kinase (BTK), PI3K, and BCL-2 and their associated pathways (**Figure A**), indicate that drug optimization is ongoing. Additionally, novel mechanisms of targeting, beyond small molecule inhibitors, are emerging as promising targets are identified. Both **antisense oligonucleotide therapy** and **degraders**—mechanisms to destroy cancer-driving proteins and production—are being assessed as single agents in Phase 1 clinical trials. Protein degraders harness the cell's natural protein-degradation machinery—the ubiquitin-proteasome system—to selectively tag unwanted or aberrantly modified proteins for destruction. Benefits of protein degraders over small molecule inhibitors include (1) reduced dosage due both to their sub-stoichiometric drug concentration necessity and their ability to target multiple copies of the protein, and (2) their potential to target proteins that were previously considered undruggable. Antisense oligonucleotides are short, synthetic, single-stranded molecules that, in this case, alter RNA so that expression of the protein is decreased. Antisense oligonucleotides are beneficial as they directly target the driver protein itself as opposed to downstream targets. As noted, it may be that the ability to modify altered protein production and/or availability leads to a more thorough and targeted therapeutic.

OPPORTUNITIES FOR RESEARCH ADVANCEMENT

Key takeaways: Accelerated movement of therapies out of the lab and into clinical trials can be bolstered by the development and incorporation of biomarkers into clinical trial design, increased biological understanding of targets, and enhanced knowledge of how tumor-immune interactions influence the efficacy of immunotherapies.

Although current drug development seems promising, barriers to ensuring optimization of therapeutic administration and efficacy remain. In addition to bespoke therapeutic development focused on targeted therapies and immunotherapy as well as identification of rational combination therapies—goals championed by FLF's CURE FL Awards grant program—expert interviews revealed additional unmet opportunities that would improve treatment and outcomes for patients with FL, specifically:

- understanding heterogeneity in patient response to therapies and customizing therapy selection accordingly;
- developing mechanisms to assess circulating tumor DNA, and perhaps RNA, acquired from minimally invasive liquid biopsies to identify tumor clones that are less responsive to therapy or predict a worse prognosis; and
- determining how immune-tumor interactions influence therapy success to drive the application of rational combination therapy strategies.

Maximizing Therapeutic Effectiveness and Reducing Resistance

FL is a heterogeneous disease, meaning it has several root causes and resulting prognoses and outcomes. Although decades of genomic studies have identified factors that influence poor prognosis, clinical behavior is not uniform. Variable clinical behavior is hypothesized to be due to genetic heterogeneity, even within subtypes and genetic groups, or host immune system-tumor interactions, which, to this point, have not been adequately studied due to limitations in animal models and patient tumor samples. Limited longitudinal tumor collection has also limited researchers' ability to identify mechanisms of drug resistance, which, in a slow-growing tumor often typified by multiple recurrences, is an essential phenomenon to understand. Moreover, biomarkers that predict drug effectiveness prior to therapy, early in the course of therapy, and in response to resistance are a critical component of achieving better outcomes in patients who do not achieve durable response or experience transformation.

Defining Cancer-Immune Cell Interactions to Improve Immunotherapy

With the increasing reliance on immunotherapies to treat FL, there is a need to better define the role of the microenvironment, specifically the immune environment (which is poorly defined in FL) in treatment effectiveness and selection. Although there has been a significant uptick in this research over the past year (Han et al. 2022; Iaccarino et al. 2022; Los-de Vries et al. 2022) [and reviewed in (Kumar, Pickard, and Okosun

2021; Amin and Braza 2022)], lack of adequate animal models that recapitulate the tumor within the lymph node environment and lack of patient tissue samples are barriers to achieving a complete understanding of these interactions and how therapeutic efficacy is impacted by tumor-immune interactions.

Optimizing Clinical Trials with Biomarker Incorporation and Design Innovation

As mentioned previously in this report, two therapeutics for FL have been removed from the market due to the inability of sponsors to perform confirmatory clinical trials after receipt of advanced approval. FL is a rare disease, diagnosed in approximately 15,000 individuals in the US each year (National Cancer Institute 2022). Additionally, the heterogeneity of the disease further subdivides patient populations, especially when assessing targeted therapies. With 201 current clinical trials for FL and a need for hundreds of patients for rigorous trial assessment, meeting enrollment requirements can be challenging for FL clinical trials. Trials should be designed to focus on identifying patients who will benefit from specific therapies, especially for high-risk patients, requiring the integration of biomarkers and patient stratification and movement toward a well-defined treatment period as opposed to anticipating prolonged or indefinite therapy.

Experts interviewed for this report also highlighted the need for more rapid and well-defined clinical trial endpoints. Current trials can extend to more than 10 years, costing significant time and money to trial sponsors, decreasing the impetus to conduct trials in FL compared to faster-growing non-indolent cancers. FDA has proposed more stringent survival endpoints, which likely will further decrease initiatives in FL. There is a significant need for response and minimal-residual disease biomarkers that enable a more rapid assessment of therapeutic effectiveness so that patients are not subjected to longer treatment periods than necessary, and sponsors can identify futility or superiority earlier.

FUTURE DIRECTIONS

Provided by FLF Chief Medical Officer Mitchell Smith in response to this assessment.

Because a key goal of the FLF is to seek curative treatment for FL, we ask “what will it take to cure FL?” Clearly, ongoing development of new therapies that are more effective, less toxic, and targeted to specific patients will help. Getting the right treatment to the right patient at the right time is important.

Improved molecular understanding of drivers of FL heterogeneity would permit therapy targeted to aggressive disease, while understanding mechanisms of resistance would enable us to apply targeted therapy to prevent or overcome such resistance. Thus, along with novel treatments, biomarker development, which will come through large, prospective linked clinical and genomic databases, will be critical.

T cell engaging therapies, both engineered T cells and antibodies that engage T cells, are exciting developments in B cell lymphoma, including FL. Better ways to engineer, grow, and target T cells will improve safety, efficacy, and accessibility. Other immune cells such as NK cells may play a role. Understanding the host immune system and lymphoma microenvironment should enhance the use of immunotherapies.

Epigenetic alterations are now known to be important in FL. Although drug development in this area has lagged, as we know more about these complex systems, targeted therapies applied to patients with specific mutations are likely to be developed. In analogous fashion, programmed cell death pathways involving the BCL2 gene family are attractive therapeutic targets, and more effective agents may be developed as we understand more about these complex systems.

It is possible that newer treatments, such as T cell directed therapies available now, are curing some patients, but we currently have no way of knowing that they are cured. Advances in molecular monitoring technology may provide such documentation and tell us the characteristics of resistant cells when cure is not achieved.

Research is proceeding in each of the above areas, often for B cell lymphoma in general, less commonly focused on FL.

Additional resources that would bolster drug development and more rapidly identify the safest, most effective, personalized therapies for FL patients, include the following:

- biorepositories housing longitudinal FL samples that are molecularly and clinically annotated, and/or biodata with clinical linkage;
- biomarkers to assess prognosis, therapy efficacy, and clinical trial endpoints, initially on tissue samples but eventually applicable to minimally invasive “liquid biopsies”; and
- *in vivo* or other models that more closely recapitulate both the heterogeneity of FL as well as the tumor cell microenvironment.

Armed with these tools, researchers will be able to more effectively address current barriers to therapy development for the most at-risk FL patients and modify treatment strategies to reduce side effects and late effects from unnecessary treatments in patients who are highly responsive to first-line therapy.

CONCLUSION

Currently, only nine therapies are approved for use in FL, and several setbacks with targeted therapy withdrawal in 2022 have created concern about PI3K inhibitors specifically. Given FDA guidance stressing the need for overall survival endpoints, a high standard, there may be more difficulties in approvals for other FL therapies moving forward. Nonetheless, a robust clinical trial landscape indicates preclinical research is vastly expanding therapeutic targets and modalities and driving toward an influx of new therapies in the clinic in the next five to 10 years. With expanding options come challenges of deciding which ones to pursue given limited patients available for trials. While there is hope on the horizon, there are patient populations, particularly those that progress within two years of therapy, that clearly require more personalized stratification and therapy selection than currently provided.

This assessment indicates drug development efforts should focus on (1) identifying more effective first-line therapies for high-risk patients, preferably based on biologic understanding; (2) employing curative approaches, most likely for patients at the time of first relapse; (3) segmenting patients who achieve durable remission from those destined for several lines of therapy; and (4) ensuring that therapies delivered to patients requiring multiple therapy types are personalized to their tumors and microenvironment and for which the probability of drug resistance and toxicity are lower. The most effective protocols will likely require rational drug combinations and integration of biomarkers to assess effectiveness early during therapy. A focus on developing innovative clinical trials that address the aforementioned goals will bring us closer to a cure for patients diagnosed with FL.

GLOSSARY

Unless otherwise noted, definitions are sourced from the NCI Dictionary of Cancer Terms.

First-Line Treatment: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation.

Heterogeneous: Composed of elements or ingredients that are not alike.

Marketing Authorization: The approval needed to place a medicinal product on the market. It sets out the medical conditions (known as indications), patient population, and dosage for which the product is authorized as well as any conditions imposed on the holder of the marketing authorization. (Source: LexisNexis)

Relapse: The return of a disease or the signs and symptoms of a disease after a period of improvement.

Remission: A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although cancer still may be in the body.

Translocation: A genetic change in which a piece of one chromosome breaks off and attaches to another chromosome. Sometimes pieces from two different chromosomes will trade places with each other.

APPENDIX

Clinical Trial Identification and Assessment

The section Current Follicular Lymphoma Clinical Trials is an assessment of clinical trial records from clinicaltrials.gov. Records were pulled on 9/16/2022 and 10/7/2022. An Advanced Search was performed with the following criteria:

- Condition or Disease: Follicular Lymphoma
- Study Type: Interventional Studies (Clinical Trials)
- Recruitment Status: Not yet recruiting; Recruiting; Enrolling by invitation; Active, not recruiting
- Phase: Early Phase 1, Phase 1, Phase 2, Phase 3, Phase 4

Two hundred and one clinical trials were included in the final assessment presented in the report.

Clinical Trial Basics

A clinical trial is research using consenting human volunteers to receive interventions such as drugs or devices, administered by researchers who follow an FDA-approved protocol to generate new medical knowledge. Despite a relative paucity of approved drugs for FL, clinical research is highly active. There are a variety of clinical trial types, including prevention, screening, diagnostic, treatment, behavioral, and quality of life trials. Treatment trials, also known as interventional trials, test new treatments, combinations, or approaches to surgery or radiation therapy and are the focus of this report. Clinical trials are conducted in a series of steps, called "phases." Each phase progresses the necessary knowledge to either move to the next phase or discontinue the clinical assessment of a therapeutic or combination therapy.

- **Phase 1 Clinical Trials** assess a treatment in a small group of people to determine the best dose of a treatment based on safety and side effects. Generally, a Phase 1 clinical trial is conducted in 20–80 individuals over several months.
- **Phase 2 Clinical Trials** assess a treatment in a larger group of people, usually with a defined disease state, to determine the effectiveness of the therapy and further study its safety. A typical Phase 2 clinical trial is conducted in approximately 50–200 people over a period of up to two years.

- **Phase 3 Clinical Trials** assess the treatment in a large group of people to confirm its effectiveness, comparing it with standard or similar treatments, generally randomized. These studies, usually conducted in 1,000–3,000 individuals over one to four years, will determine whether the therapy is either more effective or safe than currently approved and available therapies. These trials are considered the highest level of evidence to change the standard of care.
- **Phase 4 Clinical Trials** enable researchers to track the safety of a treatment in the general population, establishing more information about its benefits and optimal use. Phase 4 clinical trials take place after the treatment is approved by the FDA, or each country's regulatory authority.

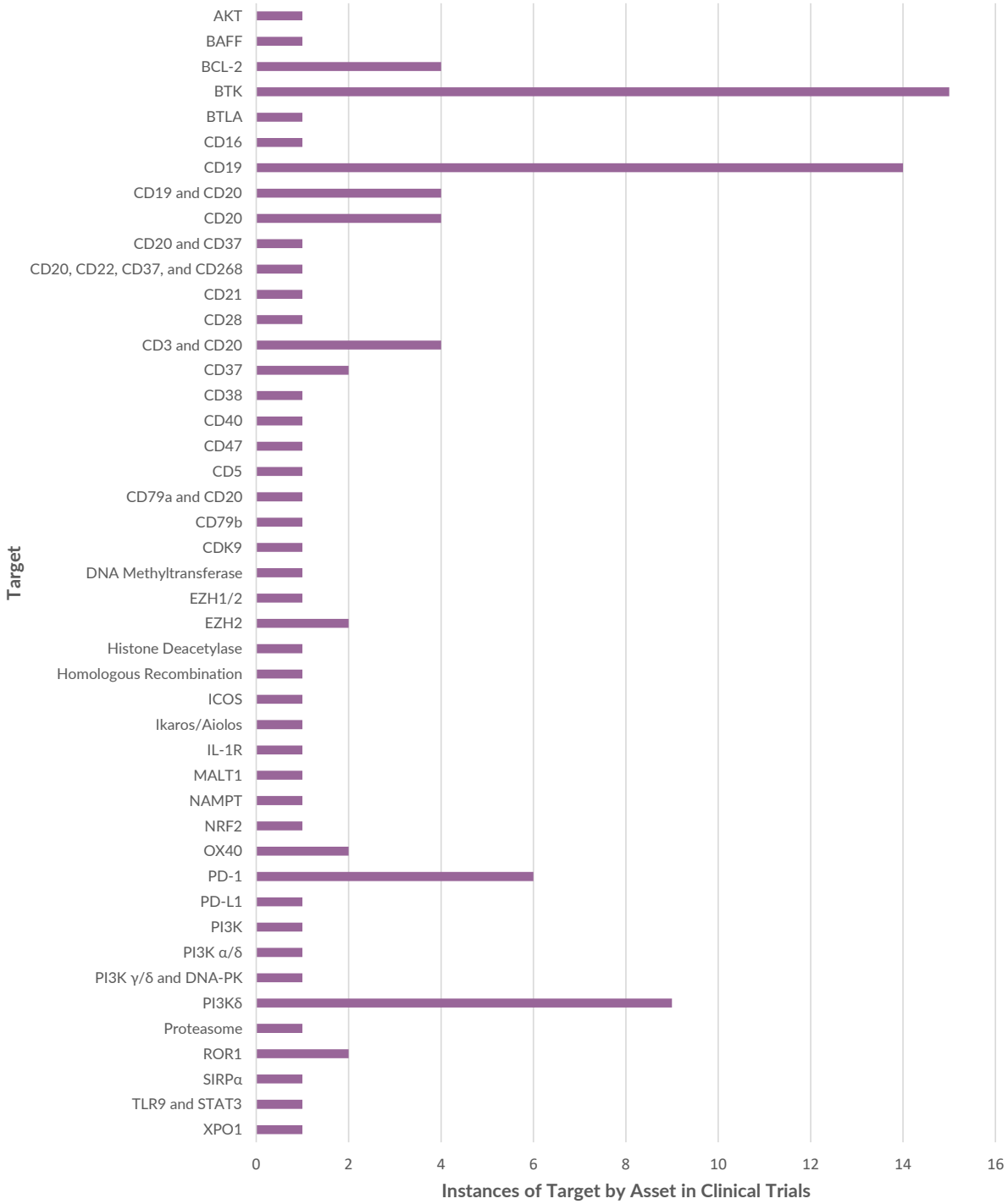
Figures and Tables

Table A: Antibody-Drug Conjugates and Radioimmunoconjugates in Clinical Trials, Highlighting Targets and Therapy Elements

Class	Therapy Name	Antibody Target	Therapeutic Agent
Antibody-Drug Conjugate	ABBV-319	CD19	glucocorticosteroid
	IKS03	CD19	pyrrolobenzodiazepine pro-drug
	STRO-001	CD74	maytansinoid
	Zilovertamab vedotin	ROR1	monomethyl auristatin E
	Polatuzumab vedotin	CD79b	monomethyl auristatin E
	Loncastuximab tesirine	CD19	SG3199
	Brentuximab vedotin	CD30	monomethyl auristatin E
Radioimmunoconjugate	Betalutin	CD37	satetraxetan
	Yttrium Y-90 ibritumomab tiuxetan	CD20	yttrium-90

Source: Milken Institute analysis of clinicaltrials.gov (2022)

Figure A. Clinical Trial Assets by Target



Note: Instances in which unique assets are under assessment in clinical trials, organized by target. Replicate assets are not included in this analysis.

Source: Milken Institute analysis of clinicaltrials.gov (2022)

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