Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: November 30, 2023

Citation: Alhaj Moustafa, M. and El Hayek, M. 2023. A Comprehensive Review of Monoclonal Antibodies for the Treatment of Follicular Lymphoma Including Both Approved and Investigational Options. Medical Research Archives, [online] 11(11). https://doi.org/10.18103/mra.v11i11.4745

DOI: https://doi.org/10.18103/mra.v11i11.4745

ISSN: 2375-1924

RESEARCH ARTICLE

A Comprehensive Review of Monoclonal Antibodies for the Treatment of Follicular Lymphoma Including Both Approved and Investigational Options

Mario El Hayek, MD[1], Muhamad Alhaj Moustafa, MD, MS[2*]

1 University of Florida College of Medicine, Gainesville, Florida
2 Mayo Clinic, Jacksonville, Florida

* alhajmoustafa@gmail.com

ABSTRACT

Follicular lymphoma (FL) is the most common type of indolent lymphoma in the Western world, accounting for approximately 30% of lymphoma cases. FL is known for its recurrent nature, necessitating diverse treatment options. The introduction of rituximab, an anti-CD20 antibody, has greatly improved FL outcomes and paved the way for targeted therapies. In this review, we thoroughly explore the structure, mechanism of action, clinical outcomes, and side effects of currently approved monoclonal antibodies (mAb) for FL. Furthermore, we provide insights into ongoing clinical trials and emerging monoclonal antibodies that hold promise for the future of FL treatment. A comprehensive literature search was conducted using various medical databases, including ASH and ASCO publications, as well as PubMed. The clinicaltrials.gov website was used to compile a list of investigational monoclonal antibodies from ongoing clinical trials. The future of antibody-based therapy for follicular lymphoma shows great promise, with a focus on enhancing antibody efficacy, prioritizing optimized combination therapies to address treatment resistance, and evaluating bispecific antibodies as first-line therapies, all while carefully balancing risks and benefits and sequencing treatments appropriately for better disease management. These directions have the potential to establish antibodies as a central component of follicular lymphoma treatment.

Introduction

Follicular lymphoma (FL) is the second most common type of lymphoma diagnosed in the United States and Western Europe.[1] It is the most prevalent form of indolent lymphoma in Western countries,[2] accounting for approximately 30% of all lymphomas.[3] Its incidence is about 4 cases per 100,000 in the United States,4 and the median age at presentation is 60 years.[1] Follicular lymphoma is characterized by a remitting and recurring course requiring multiple lines of treatment.[5] Various management modalities are available for FL including a simple watchful observation,[6] use of monoclonal antibodies,[7] chemotherapy,[8] immunotherapy,[9] chimeric antigen receptor T-cell (CAR-T),[10] as well as consolidation with hematopoietic stem cell transplantation[11] and most recently bispecific antibodies.[12] The introduction of the anti-CD20 antibody, rituximab, more than 2 decades ago, has revolutionized the treatment landscape,[13] significantly improved the outcomes, and paved the way for targeted therapies.[14] Since then, multiple monoclonal antibodies emerged with various targets.[15, 16, 17]

In this comprehensive review, we describe the structure, mechanism of action, clinical outcomes, and common side effects of the currently approved monoclonal antibodies in the treatment of FL. We also provide an update to the literature on published clinical trials addressing novel monoclonal antibodies in FL. In addition, we sought to enlighten the scientific community on potential future-generation monoclonal antibodies that are currently being investigated in clinical trials.

Methods

This comprehensive review entails in its first part a general description of monoclonal antibodies and their role in the treatment of malignancies. We then provide a comprehensive review on the four approved monoclonal antibodies for the treatment of FL. In the third part, we briefly discuss novel monoclonal antibodies that are currently being investigated for potential use in the treatment of FL.

Literature search was done on multiple electronic and medical databases, including the American Society of Hematology (ASH) publications database, and American Society of Clinical Oncology (ASCO) publications database, and PubMed. The list of investigational monoclonal antibodies from ongoing clinical trials was retrieved from the clinicaltrials.gov website. Trials investigating a novel monoclonal antibody in patients with non-Hodgkin's lymphoma and reporting separate results for the FL subgroup were included. Both finished and ongoing trials of interest were considered in this review.

I. MONOCLONAL ANTIBODIES: GENERALITIES AND THERAPEUTIC USE IN HEMATOLOGIC MALIGNANCIES

Antibodies, or immunoglobulins, are specialized key molecules of the humoral immune system that are secreted by plasma cells.[18] They are naturally present in blood and tissue fluids, and their primary role is to neutralize foreign bodies (antigens). The basic structure of an antibody consists of four polypeptide chains, two light (L) chains, and two heavy (H) chains, held together to form a "Y" shaped tetramer [19] (Fig. 1, A). The role of the two upper tips (Fab domain) is to recognize and bind various antigens, such as bacteria, or in cancer cases, malignant cells. This upper region is known as the variable region, as its composition differs across all antibodies. The remaining lower part (Fc domain), known as the effector region, interacts with other immune cells or serum proteins to ensure appropriate eradication of the foreign substance. In contrast to the variable region, the Fc domain is a constant region. It is relatively unchanged across the majority of antibodies. Adding the term 'monoclonal' implies that the antibodies are produced from a single cell lineage through cloning of unique plasma cells, inferring specificity of monoclonal antibodies (mAb) to one precise antigen. The development of monoclonal antibodies (mAb) as therapeutic agents began in 1975 by two researchers, César Milstein and Georges Köhler,[20] for which they received the Nobel prize for Physiology or Medicine in 1984. Nowadays, mAbs are used to diagnose[21] and treat several disorders, such as inflammatory conditions,[22] neurologic diseases like multiple sclerosis,[23] infections like COVID-19,[24] and malignancies.[25] In fact, their therapeutic use in lymphomas has been a cornerstone. The CD20 antigen, expressed on normal mature B-cells, contributes to the growth and activation of B-cells, and is expressed in over 90% of all B-cell non-Hodgkin's lymphomas.[26] Therefore, anti-CD20 monoclonal antibodies are a perfect therapeutic tool that is used to eliminate malignant B-cells through initiating a cascade of

events leading to apoptosis or cell lysis of cells with a CD20 receptor on their surface.[27] To date, several mAb are being used in the treatment of non-Hodgkin lymphoma. Our review will focus only on monoclonal antibodies used in the treatment of FL.

II. APPROVED MONOCLONAL ANTIBODIES IN THE TREATMENT OF FOLLICULAR LYMPHOMA

A) RITUXIMAB

Rituximab is an anti-CD20 human/murine chimeric, glycosylated immunoglobulin (Ig) containing murine light (L) - and heavy (H) - chain variable regions, and human kappa and human IgG1 constant regions.[27] (Fig.1, B) Rituximab works by inducing the killing of CD20 positive cells, through 'labeling' cells covered by the transmembrane CD20 antigen and 'displaying' them to the immune system. This is achieved through one of two different mechanisms, either by immune mobilization or by direct effects.[28] In the immune mobilizing mechanisms, rituximab initiates a cascade of events that lead to complement mediated cytotoxicity (CDC) and antibody dependent cell-mediated cytotoxicity (ADCC). Direct mechanisms, mediated through binding of rituximab to its CD20 target, inducing inhibition of proliferation, induction of apoptosis, and sensitization of cancerous cells to chemotherapy, such as cisplatin and doxorubicin.[29] Malignant B-cells covered by rituximab are also targets for phagocytosis by macrophages. While all of the previously mentioned mechanisms have been well described in vitro,[27,30] it is still not clear which one predominates in vivo.

Intravenous (IV) rituximab was granted approval in 1997 by the Food and Drug Administration (FDA) for use in relapsed/refractory indolent non-Hodgkin lymphoma (NHL). It was the first mAb to gain approval for therapeutic use in cancer, laying the foundations for a completely new oncologic class of drugs. In fact, it is not unreasonable to claim that the improvement in survival of patients with FL in the last two decades was largely due to rituximab.[31]

The benefits of rituximab added to chemotherapeutic agents in the initial treatment of advanced-stage FL has been well-established in several clinical trials.[32,33,34,35,36] These trials revealed improved response rates, time to progression, and overall survival (OS) in the rituximab plus chemotherapy arms, compared to the chemotherapy without rituximab control arms. Rituximab was also studied as a single initial therapy in patients with FL.[37,38,39] Results revealed an objective response rate (ORR) of approximately 70% and complete remission (CR) of over 30%. Additionally, rituximab is used as maintenance therapy in FL, and this has been examined in a large, randomized trial, the PRIMA phase III trial.[40] Patients who received rituximab maintenance after induction chemoimmuno-therapy therapy had a significantly higher progression-free survival (PFS) when compared to observation (10.5 years vs. 4.1 years, respectively, p-value <0.01). Extended use of rituximab in the treatment of relapsed FL was associated with better outcomes in both chemotherapy-naïve and relapse/refractory disease as examined in the SAKK 35/98 trial,[41] where 27% of disease responders remined in remission after 8 years. The common side effects of rituximab include but are not limited to infusion reactions such as fever, skin rash, angioedema, hypotension, anaphylaxis; as well as infections and infection reactivation such as hepatitis B reactivation, cytopenia, and gastrointestinal upset.[42]

B) OBINUTUZUMAB

Approved in February 2016 by the FDA, obinutuzumab is a second-generation (type II) anti-CD20 mAb. It was initially developed to address the need for novel therapeutics, potentiate the activity of anti-CD20 mAbs, and overcome resistance against the first-generation (type I) mAb rituximab.[43] Its main structural difference compared to rituximab is a post-translational glycoengineering process that results in the absence of a fucose sugar residue from the Fc portion, effector region, rendering this new modified mAb to acquire increased affinity in binding immune effector cells.[44,45] (Fig.1, C) Additionally, obinutuzumab has an altered amino acid sequence, compared to first-generation anti-CD20 mAbs, which results in spatial alterations of the CD20 - mAb complex on B-cells.[45,46] There are differences in mechanism of action of second-generation mAbs compared to that of first-generation mAbs. Obinutuzumab enhances direct cell death (DCD), ADCC, and antibody-dependent cell-mediated phagocytosis (ADCP), while decreasing CDC. By comparison, rituximab works predominantly via CDC and ADCC/ADCP, with DCD contributing to a much lesser extent to the mechanism of action.[47]

Obinutuzumab was evaluated in a phase III study comparing chemoimmunotherapy with either obinutuzumab or rituximab in previously untreated patients with FL followed by 2 years of maintenance with either obinutuzumab or rituximab.[15] Although, PFS was better for patients receiving obinutuzumab (estimated 3-year PFS of 80.0% with obinutuzumab vs. 73.3% with rituximab), the response rates and OS were similar. In addition, adverse events of grades 3 to 5 were seen more frequently in the obinutuzumab group than in the rituximab group (74.6% vs. 67.8%), as were serious adverse events (46.1% in the obinutuzumab arm vs. 39.9% in the rituximab arm). Also, a phase I study testing obinutuzumab in combination with chemotherapy showed 98% response rate in relapsed and refractory FL.[48] Nevertheless, when compared to type I mAbs, the main concern with obinutuzumab remains its toxicity. In a very recent systematic review and meta-analysis, Amitai et. al explored adverse events in all randomized clinical trials comparing obinutuzumab-based regimens to rituximab-based regimens.[49] In this study, obinutuzumab-based regimens had statistically significant increased rates of grade III-IV adverse events as well as grade III-IV toxicities including thrombocytopenia, infusion-related reactions, and cardiac events when compared to rituximab-based regimens. Thus, in clinical practice, rituximab is still used more frequently in the initial lines of therapy, and obinutuzumab is reserved for rituximab-refractory cases.

C) IBRITUMOMAB-TIUXETAN

90-Y-Ibritumomab-Tiuxetan (90Y-IT), an anti-CD20 mAb - drug conjugate, is a form of targeted radiation therapy, or radioimmuno-therapy. It was granted its first FDA approval in 2002. The anti–CD20 mAb ibritumomab is covalently linked to the chelator tiuxetan, to which is further added the radioactive isotope, yttrium-90 (90Y). (Figure 1, D) The mAb ibritumomab labels its CD20 antigen target on the B-cell surface delivering the isotope 90Y which emits beta radiation and induces cellular damage by forming free radicals in the target and neighboring cells.[50] A phase III clinical trial comparing 90Y-IT to observation following a complete or partial remission to induction chemotherapy for treating naïve patients with FL reported that at 8 years, patients had a median improvement in PFS of approximately 36 months with 90Y-IT.51 Published in 2002, one of the pivotal studies that led to the FDA approval of this mAb – drug conjugate in relapsed refractory FL was a Phase II clinical trial in patients with low-grade FL who were refractory to rituximab.[52] Overall response was 74% with a CR of 15%; the median duration of response was around 6.4 months. 90Y-IT has been also used as a first line therapy in FL with a PFS of 38.3% at 8-year follow up.53 A cost-effectiveness analysis of 90Y-IT compared to the standard of care, bendamustine and rituximab (BR) showed no differences between the two treatment arms in terms of ORR, CR rate and 5-years PFS.[54] However, patients treated with 90Y-IT required an average of 4.5 fewer oncology clinic visits, an average of 10 fewer days of therapeutic use, and 40% less use of growth factors, as compared to the BR group within the first year of treatment. Furthermore, the direct therapeutic cost of 90Y-IT was 54% less than that of 6 cycles of BR. The main short-term toxicity of this agent is bone marrow suppression. Other side effects include serious infusion reactions, and severe cutaneous and mucocutaneous reactions. This agent is underutilized due to the logistic challenges and the need for multi-specialty (nuclear medicine/radiation oncology and medical oncology) coordination to administer the drug. Thus, its use is limited mainly to certain academic centers.

D) MOSUNETUZUMAB-AXGB

Mosunetuzumab-axgb was awarded an accelerated approval by the FDA on December 22, 2022. It is a bispecific mAb, with one Fab segment directed towards CD20, and the other Fab segment directed towards CD3 (a receptor present on the surface of T-cells). (Figure 1, E) Therefore, bispecific antibodies, such as Mosunetuzumab-axgb, are molecules that can recognize and bind two different targets simultaneously, bringing two different cells into proximity. This leads effector cells, such as T-cells in this case, to directly exert cytotoxic effects on targeted B-cells.[55] Mosunetuzumab-axgb is indicated in the treatment of adult patients with relapsed/refractory FL after two or more lines of systemic therapy.[17] The efficacy of this mAb was evaluated in a phase II multicenter, multi-cohort study in patients with relapsed/refractory FL who had undergone at least two prior therapies.[56] Among 90 patients enrolled, the ORR was 80%, with 60% achieving complete response. Only 3/90 (3%) of the study participants had been treated with chimeric antigen receptor T cell

(CAR-T cell) prior to Mosunetuzumab. Furthermore, this agent is being currently tested in patient with previously untreated FL in three separate ongoing clinical trials, in combination with tazemetostat (NCT05994235), polatuzumab vedotin (NCT05410418), and lenalidomide (NCT04792502). The drug also displayed a favorable safety profile. Although cytokine releases syndrome (CRS) was a commonly encountered side effect in this multicenter study (38/90 patients, 42%), it was predominantly Grade I or II, with only two patients (2%) having Grade III or IV CRS. Median time to CRS onset was 5 hours on day 1, 20 hours on day 8, and 27 hours on day 15 of cycle 1; with a median total duration of 3 days. Incidence of grade III-IV CRS with Mosunetuzumab (1%) was lower than the 6% incidence seen in the pivotal Zuma-5 trial testing axicabtagene ciloleucel,[57] an approved CAR-T cell therapy in FL. Besides CRS, immune effector cell associated neurotoxicity syndrome (ICANS), a potentially life-threatening adverse effect, was seen in only 5% of patients treated with Mosunetuzumab; all the cases were grade I or II and eventually resolved.[56] However, grade III-IV neurological toxicity was seen in 15% of patients with FL treated with axicabtagene ciloleucel. In addition, two meta-analyses were done to investigate the incidence of ICANS following CAR-T cell therapy administration; one reported an incidence of 37.2%[58] and the other reported an incidence of 21.7%.[59] Ultimately, this implies considerable differences in the incidence of CRS and ICANS occurrences following Mosunetuzumab vs. CAR-T cell therapy. The main challenge of utilizing this agent is the need for close monitoring for CRS and neurotoxicity at least during the first cycle of treatment. This requires the patient to either be admitted to the hospital or stay in close proximity to the treating center. Thus, the uptake of bispecific antibodies might be lower in small community-based practices.

III. INVESTIGATIONAL MONOCLONAL ANTIBODIES IN THE TREATMENT OF FOLLICULAR LYMPHOMA

Multiple cellular membrane proteins, such as CD22, CD40, CD80, CD79b, and PDL-1 play a pivotal role in the pathogenesis of FL and have emerged as promising targets for its treatment. CD22 is present on the surface of B-cells and is involved in regulating B-cell activation and survival, making it an attractive target for monoclonal antibody therapies. 60 CD40, also found on B cells, interacts with CD40 Ligand, and constitutes an immune checkpoint that leads to the activation of both innate and immune cells. Because of this essential role in immune response promotion, this interaction has been regarded as an attractive immunotherapy target.[61] CD80 is another therapy target that is capable of mediating immune suppression or tolerance through interactions with CTLA4, and also through the more recently described interaction with PD-L1.[62] Thus, the expression of CD80 on malignant cells and/or nonmalignant cells present in the tumor microenvironment may support tumor progression by inhibiting innate or adaptive immune responses to tumor, hence its significance as an important treatment target. Another interesting target in FL treatment is CD79b, which is expressed on the vast majority of lymphomatous B-cells. In fact, Polatuzumab Vedotin (an anti-CD79b monoclonal antibody covalently linked to the anti-mitotic cytotoxic agent monomethyl auristatin (MMAE) via a cleavable linker) is internalized by CD79b and once inside the target cell, destroys it by stimulating apoptosis, in addition to inhibiting mitosis, tubulin, and tubulin polymerization.[63] Finally, PDL-1, a ligand present in tumor cells, interacts with PD-1 on immune cells to suppress the immune response; and inhibiting this interaction can enhance the immune system's ability to target lymphoma cells. [64]

A) Published Clinical Trials on Novel Monoclonal Antibodies

Our literature search yielded 33 clinical trials that published effective results of using novel monoclonal antibodies in treating FL. These studies were published between 2003 and 2022, with 40% published after 2019. Out of 33 trials, 7 (21%) were phase I trials and 11 (33%) were phase II trials. The overwhelming majority (93%) were single-arm clinical trials. Over half of the trials (55%) included patients with relapsed/ refractory FL, and 21 different monoclonal antibodies were assessed. Details of the published trials, including their clinical trial number, the trial phase, disease status, as well as disease outcomes such as PFS, CRR, and ORR are found in Table 1.

SINGLE TARGET ANTIBODIES EVALUATED AS SINGLE AGENTS

ANTI-CD20 ANTIBODIES

The most frequently examined category of novel monoclonal antibodies consisted of these investigated as individual agents, specifically targeting a single molecule (N = 16, 48%). Within this category, the most commonly targeted transmembrane protein was CD20, with 5 different monoclonal antibodies studied. These were Ofatumumab, Veltuzumab, Ocrelizumab, Ocaratuzumab, and LY2469298. Three different trials examined Ofatumumab, with the four remaining antibodies each examined in one trial. All trials were conducted in FL patients with R/R disease status, except for one trial examining Ofatumumab in previously untreated patients. This same trial showed high ORR compared to the other anti-CD20 antibodies used as single agents: 84%.[65] The CRR in this study was low at 9%. All other anti-CD20s used as single agents unfortunately revealed non-promising ORRs ranging from 22% to 63%. [66,67,68,69,70,71]

ANTI-CD22 ANTIBODIES

The second most commonly targeted transmembrane protein was CD22, with Epratuzumab and Inotuzumab Ozogamicin studied as single agents in one and two trials, respectively. Epratuzumab was studied in a phase I/II trial in patients with R/R FL and revealed a low ORR of 24% with a PFS of 87 weeks.[72] Inotuzumab Ozogamicin had significantly higher ORRs, reaching 68%[73] and 85%.[74] The latter study was conducted in patients that were pre-treated with Rituximab. Hence, Inotuzumab Ozogamicin seems to be a promising anti-CD22 antibody. However, severe hepatoxicity and veno-occlusive disease were related toxicities. [75]

OTHER ANTIBODIES

Loncastuximab Tesirine is an anti-CD19 that was studied as a single agent in a phase I trial in patients with R/R FL and was shown to have an ORR of 79% and a CRR reaching 65%.[76] Anti-CD38 antibody Daratumumab,[77] anti-CD40 antibody Lucatumumab,78 anti-CD80 antibody Galiximab,[79] and anti-PDL-1 Nivolumab80 were all studied in patients with R/R FL in separate trials and had relatively low ORRs, ranging from 4% with Nivolumab[80] to 33% with Lucatumumab.[78]

SINGLE TARGET ANTIBODIES EVALUATED WITH OTHER AGENTS

ANTI-CD20 ANTIBODIES COMBINATIONS

Another category of novel monoclonal antibody use comprises antibodies directed at a single target but studied in combination with other agents. Fourteen published trials (42%) tested mAbs within this category. An anti-CD20 antibody known as Tositumomab was administered to patients with FL in three different trials. Among these trials, two incorporated it in combination with CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone), while the third utilized it in conjunction with Fludarabine. Remarkably, the three mentioned combinations resulted in ORRs all ranging between 90 and 100%.[81,82,83] Ofatumumab was also examined with CHOP in previously untreated patients with FL, and revealed an ORR of 90-100% with a CRR of 62%.[67] Plausibly, utilizing anti-CD20 antibodies in combination with chemotherapy treatments, namely CHOP, yields higher response rates than when used individually.

ANTI-PDL1 ANTIBODIES COMBINATIONS

Antibodies targeting PDL-1 were also frequently tested alongside other agents, in a total of 5 published trials (Atezolizumab was used with Obinutuzumab, whereas Pembrolizumab and Pidilizumab were used with Rituximab). The best ORR achieved here was with Pembrolizumab + Rituximab in R/R FL, reaching 93%.[84]

ANTI-CD22 AND ANTI-CD79B ANTIBODIES COMBINATIONS

Epratuzumab was assessed in combination with Rituximab in two trials with ORRs of 54%[85] and 88%.[86] Two other trials assessed Polatuzumab (anti-CD79b), one with Rituximab and one with Obinutuzumab and Lenalidomide showing ORRs of 70%[87] and 76%,[88] respectively.

BISPECIFIC ANTIBODIES EVALUATED AS SINGLE AGENTS

Bispecific monoclonal antibodies are important emerging treatment modality. A significant number of agents have been studied to date. Notably, some novel bispecific antibodies have a similar mechanism of action to Mosunetuzumab-axgb, simultaneously binding CD20 on B-cells and CD3 on T-cells. These include epcoritamab, glofitamab, and odronextamab. Epcoritamab and odronextamab were examined as single agents in patients with R/R FL, and showed

promising ORRs of 90%[89] and 91%,[90] respectively. Glofitamab was also examined as a single agent with less encouraging results and an ORR of 54%.[91] It can be inferred that using bispecific antibodies as single agents may prove to be more effective than using monospecific agents alone, given that a majority of bispecific antibodies have shown higher ORRs compared to their monospecific counterparts. However, this was not validated in direct head-to-head trials. These agents are likely going to be developed and studied as single agents and in combinations with various other agents in different settings in FL.

III. B) Novel Monoclonal Antibodies Under Investigation

We identified a total of 31 ongoing trials evaluating novel monoclonal antibodies in FL on clinicaltrials.gov. The overwhelming majority of these trials are phase I or II, only one trial is in phase III. Nineteen trials (62%) are expected to be completed in the next two years (by January 2025). Further details about these ongoing trials are represented in Table 2.

SINGLE TARGET ANTIBODIES INVESTIGATED AS SINGLE AGENTS

Pembrolizumab, a PDL-1 inhibitor, is under investigation as a standalone agent in a Phase II trial. Additionally, two separate Phase I trials are currently assessing BN-301 and STRO-001, both of which are anti-CD74 antibodies. It is anticipated that both trials will be completed by the end of 2024.

SINGLE TARGET ANTIBODIES INVESTIGATED WITH OTHER AGENTS

Several monoclonal antibodies are currently under investigation in combination with different agents. Pembrolizumab is currently being evaluated in three separate trials in combination with Vorinostat, Rituximab, and NeoVax. Nivolumab, another PD-L1 inhibitor, is being investigated in conjunction with Rituximab. Brentuximab-vedotin, a CD30 drug conjugate, is being tested in combination with Bendamustine in phase II clinical trial in CD30 positive R/R FL.

BISPECIFIC ANTIBODIES INVESTIGATED AS SINGLE AGENTS

Epcoritamab and glofitamab, are being investigated in ongoing trials as single agents, with glofitamab being tested as a treatment for FL patients previously treated with Obinutuzumab. Other bispecific antibodies include Blinatumomab and TNB-486, which work through a different mechanism of action. They are both bispecific T-cell engagers (BiTE), and noteworthy for their ability to link CD19 on B-cells and CD3 on T-cells. TNB-486 is being investigated as a single agent in a phase I trial in patients with an R/R disease status. TG-1801 is another bispecific antibody targeting CD19 on B-cells and the "do not eat me" CD47 ligand expressed on the surface of tumor cells to evade macrophage-mediated phagocytosis. It is being examined in an ongoing phase IB trial that is expected to conclude towards the end of 2023.

BISPECIFIC ANTIBODIES INVESTIGATED WITH OTHER AGENTS

Bispecific antibodies appear to achieve high response rates comparable to that of CAR-T cell therapies and exhibit lower rates of serious adverse reactions such as CRS and ICANS.92 Therefore, these antibodies are expected to bring important new treatment options beyond CAR-T cell therapies, and using bispecific antibodies in earlier lines of therapy could potentially impact the outcomes of FL patients. A significant number of bispecific antibodies are presently undergoing investigation in combination with various other agents. Particularly noteworthy is one of the most promising clinical trials, which is assessing Epcoritamab in eight different arms, each paired with a distinct agent (NCT04663347). This trial is anticipated to conclude by November 2024. Blinatumomab is also being examined with Lenalidomide in patients with Rituximab refractory FL (NCT04834024).

Six of the ongoing clinical trials (19%) are examining the use of bispecific antibodies as first-line therapy (NCT03498612, NCT05788081, NCT05169658, NCT05783609, NCT04663347, NCT05783596). Additionally, combining multiple antibodies in early phases of treatment could improve efficacy, and this is being investigated in four of the ongoing trials whereby patients with FL are receiving combinations of approved and novel antibodies as first-line therapy treatments. With the expansion of the treatment armamentarium, sequencing of treatments will be challenging and should be individualized based on patient's history, prior response to treatment regimens and overall prognosis.

TRISPECIFIC ANTIBODIES (TSABS)

Despite the promising outcomes observed with monoclonal and bispecific antibodies, they continue to pose notable challenges, including relatively low response rates, treatment resistance, and the occurrence of side effects. Consequently, the scientific community has embarked on exploring the potential development of trispecific antibodies (TsAbs), with the goal of enhancing therapeutic effectiveness while mitigating side effects. Till date, no TsAbs has been approved for clinical use, however, a few are in pre-clinical stages. 93 In most designs, one of the three sites binds T or Natural Killer (NK) cells, the other binds a tumor associated antigen (TAA). For example, a CD38/CD28/CD3 trispecific antibody was developed to enhance both T-cell activation and tumor targeting.94 The engagement of both CD3 and CD28 promotes efficient T-cell stimulation, whereas the anti-CD38 domain directs T-cells to cancerous cells. Another approach enables the efficient creation of immune synapses facilitated by CD19/CD22/CD3 interactions between target cells and T cells. A well-optimized trispecific antibody (tsAb) has the potential to outperform other types of antibodies in terms of eliciting T-cell-specific cytotoxicity and cytokine production against tumor cells. It has been shown to markedly enhance anti-tumor effectiveness,95 surpassing the performance of the currently used antibodies. While this design offers improved targeting of cancerous cells, the potential for reduced resistance, and the stimulation of a potent immune response, it regrettably comes with several challenges. These include feasibility, complexity and the associated costs, safety concerns, and a limited body of data available in the literature.

Conclusion

The future of antibody-based therapy in the treatment of follicular lymphoma holds great promise. However, research and development are needed to explore innovative strategies for enhancing the efficacy of antibodies, whether through the development of multi-specific antibodies or the investigation of new target molecules. Optimizing combination therapies involving antibodies, immunotherapy, enzyme inhibitors, and chemotherapy should be a priority to tackle treatment resistance and improve patient outcomes. Additionally, bispecific antibodies are making their way to becoming first-line therapies, either as single agents or in combination with other treatments, offering new avenues for improved disease management. In an indolent type of lymphomas like FL, the challenge lies in striking the right balance between risks and benefits and sequencing treatment agents appropriately to optimize efficacy and minimize toxicity. Moreover, bispecific antibodies present an advantage in accessibility compared to CAR-T cell therapy, which is currently limited to specialized centers. As we navigate these future directions, we have the potential to further elevate the role of antibodies as a cornerstone in FL treatment.

References

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-2390. doi:10.1182/blood-2016-01-643569

2. Cerhan JR. Epidemiology of Follicular Lymphoma. Hematol Oncol Clin North Am. 2020;34(4):631-646. doi:10.1016/j.hoc.2020.02.001

3. Kaseb H, Ali MA, Koshy NV. Follicular Lymphoma. In: StatPearls. StatPearls Publishing; 2023. Accessed April 8, 2023. http://www.ncbi.nlm.nih.gov/books/NBK538206/

4. Monga N, Nastoupil L, Garside J, et al. Burden of illness of follicular lymphoma and marginal zone lymphoma. Ann Hematol. 2019;98(1):175-183. doi:10.1007/s00277-018-3501-8

5. Mozas P, Sorigué M, López-Guillermo A. Follicular lymphoma: an update on diagnosis, prognosis, and management. Med Clin (Barc). 2021;157(9):440-448. doi:10.1016/j.medcli.2021.03.041

6. Luminari S, Bellei M, Biasoli I, Federico M. Follicular lymphoma - treatment and prognostic factors. Rev Bras Hematol E Hemoter. 2012;34(1):54-59. doi:10.5581/1516-8484.20120015

7. Illidge T, Chan C. How have outcomes for patients with follicular lymphoma changed with the addition of monoclonal antibodies? Leuk Lymphoma. 2008;49(7):1263-1273. doi:10.1080/10428190802090805

8. Steffanoni S, Ghielmini M, Moccia A. Chemotherapy and treatment algorithms for follicular lymphoma: a look at all options. Expert Rev Anticancer Ther. 2015;15(11):1337-1349. doi:10.1586/14737140.2015.1092386

9. Flowers CR, Leonard JP, Nastoupil LJ. Novel immunotherapy approaches to follicular lymphoma. Hematol Am Soc Hematol Educ Program. 2018;2018(1):194-199. doi:10.1182/asheducation-2018.1.194

10. Marofi F, Rahman HS, Achmad MH, et al. A Deep Insight Into CAR-T Cell Therapy in Non-Hodgkin Lymphoma: Application, Opportunities, and Future Directions. Front Immunol. 2021;12:681984. doi:10.3389/fimmu.2021.681984

11. Bhatt VR, Armitage JO. Autologous and allogeneic hematopoietic stem cell transplantation in follicular lymphoma. Expert Opin Biol Ther. 2016;16(1):57-66. doi:10.1517/14712598.2016.1096341

12. Lin Z, Liu L, Li Z, Xu B. Bispecific antibodies as monotherapy or in combinations for non-hodgkin B-cell lymphoma: latest updates from the American society of hematology 2022 annual meeting. Exp Hematol Oncol. 2023;12(1):41. doi:10.1186/s40164-023-00404-3

13. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood. 2010;116(12):2040-2045. doi:10.1182/blood-2010-03-276246

14. van Meerten T, Hagenbeek A. Novel antibodies against follicular non-Hodgkin's lymphoma. Best Pract Res Clin Haematol. 2011;24(2):231-256. doi:10.1016/j.beha.2011.03.002

15. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med. 2017;377(14):1331-1344. doi:10.1056/NEJMoa1614598

16. Johnston PB, Bondly C, Micallef INM. Ibritumomab tiuxetan for non-Hodgkin's lymphoma. Expert Rev Anticancer Ther. 2006;6(6):861-869. doi:10.1586/14737140.6.6.861

17. Gondran C, Ysebaert L. [Drug approval: Mosunetuzumab - third-line therapy in follicular lymphoma]. Bull Cancer (Paris). 2022;109(11):1105-1106. doi:10.1016/j.bulcan.2022.07.010

18. Allen HC, Sharma P. Histology, Plasma Cells. In: StatPearls. StatPearls Publishing; 2023. Accessed April 11, 2023. http://www.ncbi.nlm.nih.gov/books/NBK556082/

19. Nelson PN, Reynolds GM, Waldron EE, Ward E, Giannopoulos K, Murray PG. Monoclonal antibodies. Mol Pathol MP. 2000;53(3):111-117. doi:10.1136/mp.53.3.111

20. Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature. 1975;256(5517):495-497. doi:10.1038/256495a0

21. Dunn DL. Monoclonal antibodies for diagnosis and treatment. Arch Surg Chic Ill 1960. 1993;128(11):1274-1280. doi:10.1001/archsurg.1993.01420230102016

22. Posner J, Barrington P, Brier T, Datta-Mannan A. Monoclonal Antibodies: Past, Present and Future. Handb Exp Pharmacol. 2019;260:81-141. doi:10.1007/164_2019_323

23. Di Pauli F, Berger T, Reindl M. Monoclonal antibodies in the treatment of multiple sclerosis. Curr Med Chem. 2009;16(36):4858-4868. doi:10.2174/092986709789909585

24. Lloyd EC, Gandhi TN, Petty LA. Monoclonal Antibodies for COVID-19. JAMA. 2021;325(10):1015. doi:10.1001/jama.2021.1225

25. Kaur N, Goyal A, Sindhu RK. Therapeutic Monoclonal Antibodies in Clinical Practice against Cancer. Anticancer Agents Med Chem. 2020;20(16):1895-1907. doi:10.2174/1871520620666200703191653

26. Yamada T. Therapeutic monoclonal antibodies. Keio J Med. 2011;60(2):37-46. doi:10.2302/kjm.60.37

27. Reff ME, Carner K, Chambers KS, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood. 1994;83(2):435-445.

28. Cerny T, Borisch B, Introna M, Johnson P, Rose AL. Mechanism of action of rituximab: Anticancer Drugs. 2002;13:S3-S10. doi:10.1097/00001813-200211002-00002

29. Alas S, Bonavida B. Rituximab inactivates signal transducer and activation of transcription 3 (STAT3) activity in B-non-Hodgkin's lymphoma through inhibition of the interleukin 10 autocrine/paracrine loop and results in down-regulation of Bcl-2 and sensitization to cytotoxic drugs. Cancer Res. 2001;61(13):5137-5144.

30. Golay J, Zaffaroni L, Vaccari T, et al. Biologic response of B lymphoma cells to anti-CD20 monoclonal antibody rituximab in vitro: CD55 and CD59 regulate complement-mediated cell lysis. Blood. 2000;95(12):3900-3908.

31. Jacobsen E. Follicular lymphoma: 2023 update on diagnosis and management. Am J Hematol. 2022;97(12):1638-1651. doi:10.1002/ajh.26737

32. Herold M, Haas A, Srock S, et al. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. J Clin Oncol Off J Am Soc Clin Oncol. 2007;25(15):1986-1992. doi:10.1200/JCO.2006.06.4618

33. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2005;106(12):3725-3732. doi:10.1182/blood-2005-01-0016

34. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood. 2005;105(4):1417-1423. doi:10.1182/blood-2004-08-3175

35. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol Off J Am Soc Clin Oncol. 2008;26(28):4579-4586. doi:10.1200/JCO.2007.13.5376

36. Salles G, Mounier N, de Guibert S, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. Blood.

2008;112(13):4824-4831. doi:10.1182/blood-2008-04-153189

37. Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. Blood. 2001;97(1):101-106. doi:10.1182/blood.v97.1.101

38. Ghielmini M, Schmitz SFH, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood. 2004;103(12):4416-4423. doi:10.1182/blood-2003-10-3411

39. Witzig TE, Vukov AM, Habermann TM, et al. Rituximab therapy for patients with newly diagnosed, advanced-stage, follicular grade I non-Hodgkin's lymphoma: a phase II trial in the North Central Cancer Treatment Group. J Clin Oncol Off J Am Soc Clin Oncol. 2005;23(6):1103-1108. doi:10.1200/JCO.2005.12.052

40. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet Lond Engl. 2011;377(9759):42-51. doi:10.1016/S0140-6736(10)62175-7

41. Martinelli G, Schmitz SFH, Utiger U, et al. Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98. J Clin Oncol Off J Am Soc Clin Oncol. 2010;28(29):4480-4484. doi:10.1200/JCO.2010.28.4786

42. Hanif N, Anwer F. Rituximab. In: StatPearls. StatPearls Publishing; 2023. Accessed April 15, 2023. http://www.ncbi.nlm.nih.gov/books/NBK564374/

43. Freeman CL, Sehn LH. A tale of two antibodies: obinutuzumab versus rituximab. Br J Haematol. 2018;182(1):29-45. doi:10.1111/bjh.15232

44. Goede V, Klein C, Stilgenbauer S. Obinutuzumab (GA101) for the treatment of chronic lymphocytic leukemia and other B-cell non-hodgkin's lymphomas: a glycoengineered type II CD20 antibody. Oncol Res Treat. 2015;38(4):185-192. doi:10.1159/000381524

45. Mössner E, Brünker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood. 2010;115(22):4393-4402. doi:10.1182/blood-2009-06-225979

46. Niederfellner G, Lammens A, Mundigl O, et al. Epitope characterization and crystal structure of GA101 provide insights into the molecular basis for type I/II distinction of CD20 antibodies. Blood. 2011;118(2):358-367. doi:10.1182/blood-2010-09-305847

47. Suresh T, Lee LX, Joshi J, Barta SK. New antibody approaches to lymphoma therapy. J Hematol OncolJ Hematol Oncol. 2014;7:58. doi:10.1186/s13045-014-0058-4

48. Radford J, Davies A, Cartron G, et al. Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). Blood. 2013;122(7):1137-1143. doi:10.1182/blood-2013-01-481341

49. Amitai I, Gafter-Gvili A, Shargian-Alon L, Raanani P, Gurion R. Obinutuzumab-related adverse events: A systematic review and meta-analysis. Hematol Oncol. 2021;39(2):215-221. doi:10.1002/hon.2828

50. Riley MB. Ibritumomab tiuxetan. Clin J Oncol Nurs. 2003;7(1):110-112. doi:10.1188/03.CJON.109-112

51. Morschhauser F, Radford J, Van Hoof A, et al. 90Yttrium-ibritumomab tiuxetan consolidation of first remission in advanced-stage follicular non-Hodgkin lymphoma: updated results after a median follow-up of 7.3 years from the International, Randomized, Phase III First-LineIndolent trial. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(16):1977-1983. doi:10.1200/JCO.2012.45.6400

52. Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J

Clin Oncol Off J Am Soc Clin Oncol. 2002;20(15):3262-3269. doi:10.1200/JCO.2002.11.017

53. Rieger K, De Filippi R, Lindén O, et al. 90-yttrium-ibritumomab tiuxetan as first-line treatment for follicular lymphoma: updated efficacy and safety results at an extended median follow-up of 9.6 years. Ann Hematol. 2022;101(4):781-788. doi:10.1007/s00277-022-04781-3

54. Alhaj Moustafa M, Borah BJ, Moriarty JP, et al. Yttrium-90 Ibritumomab Tiuxetan is Cost-Effective Compared to Bendamustine + Rituximab in Low-grade Lymphomas. Clin Lymphoma Myeloma Leuk. 2023;23(4):259-265. doi:10.1016/j.clml.2023.01.010

55. Salvaris R, Ong J, Gregory GP. Bispecific Antibodies: A Review of Development, Clinical Efficacy and Toxicity in B-Cell Lymphomas. J Pers Med. 2021;11(5):355. doi:10.3390/jpm11050355

56. Budde LE, Sehn LH, Matasar M, et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. Lancet Oncol. 2022;23(8):1055-1065. doi:10.1016/S1470-2045(22)00335-7

57. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2022;23(1):91-103. doi:10.1016/S1470-2045(21)00591-X

58. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. J Immunother Cancer. 2018;6(1):56. doi:10.1186/s40425-018-0343-9

59. Grigor EJM, Fergusson D, Kekre N, et al. Risks and Benefits of Chimeric Antigen Receptor T-Cell (CAR-T) Therapy in Cancer: A Systematic Review and Meta-Analysis. Transfus Med Rev. 2019;33(2):98-110. doi:10.1016/j.tmrv.2019.01.005

60. Nitschke L. The role of CD22 and other inhibitory co-receptors in B-cell activation. Curr Opin Immunol. 2005;17(3):290-297. doi:10.1016/j.coi.2005.03.005

61. Tang T, Cheng X, Truong B, Sun L, Yang X, Wang H. Molecular basis and therapeutic implications of CD40/CD40L immune checkpoint. Pharmacol Ther. 2021;219:107709. doi:10.1016/j.pharmthera.2020.107709

62. Dakappagari N, Ho SN, Gascoyne RD, Ranuio J, Weng AP, Tangri S. CD80 (B7.1) is expressed on both malignant B cells and nonmalignant stromal cells in non-Hodgkin lymphoma. Cytometry B Clin Cytom. 2012;82(2):112-119. doi:10.1002/cyto.b.20631

63. Deeks ED. Polatuzumab Vedotin: First Global Approval. Drugs. 2019;79(13):1467-1475. doi:10.1007/s40265-019-01175-0

64. Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. Am J Cancer Res. 2020;10(3):727-742.

65. Rosenbaum CA, Jung SH, Pitcher B, et al. Phase 2 multicentre study of single-agent ofatumumab in previously untreated follicular lymphoma: CALGB 50901 (Alliance). Br J Haematol. 2019;185(1):53-64. doi:10.1111/bjh.15768

66. Hagenbeek A, Gadeberg O, Johnson P, et al. First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase 1/2 trial. Blood. 2008;111(12):5486-5495. doi:10.1182/blood-2007-10-117671

67. Czuczman MS, Fayad L, Delwail V, et al. Ofatumumab monotherapy in rituximab-refractory follicular lymphoma: results from a multicenter study. Blood. 2012;119(16):3698-3704. doi:10.1182/blood-2011-09-378323

68. Morschhauser F, Leonard JP, Fayad L, et al. Humanized anti-CD20 antibody, veltuzumab, in refractory/recurrent non-Hodgkin's lymphoma: phase I/II results. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27(20):3346-3353. doi:10.1200/JCO.2008.19.9117

69. Morschhauser F, Marlton P, Vitolo U, et al. Results of a phase I/II study of ocrelizumab, a fully humanized anti-CD20 mAb, in patients with relapsed/refractory follicular lymphoma. Ann Oncol Off J Eur Soc Med Oncol.

2010;21(9):1870-1876. doi:10.1093/annonc/mdq027

70. Tobinai K, Ogura M, Kobayashi Y, et al. Phase I study of LY2469298, an Fc-engineered humanized anti-CD20 antibody, in patients with relapsed or refractory follicular lymphoma. Cancer Sci. 2011;102(2):432-438. doi:10.1111/j.1349-7006.2010.01809.x

71. Ganjoo KN, de Vos S, Pohlman BL, et al. Phase 1/2 study of ocaratuzumab, an Fc-engineered humanized anti-CD20 monoclonal antibody, in low-affinity FcγRIIIa patients with previously treated follicular lymphoma. Leuk Lymphoma. 2015;56(1):42-48. doi:10.3109/10428194.2014.911859

72. Leonard JP, Coleman M, Ketas JC, et al. Phase I/II trial of epratuzumab (humanized anti-CD22 antibody) in indolent non-Hodgkin's lymphoma. J Clin Oncol Off J Am Soc Clin Oncol. 2003;21(16):3051-3059. doi:10.1200/JCO.2003.01.082

73. Advani A, Coiffier B, Czuczman MS, et al. Safety, pharmacokinetics, and preliminary clinical activity of inotuzumab ozogamicin, a novel immunoconjugate for the treatment of B-cell non-Hodgkin's lymphoma: results of a phase I study. J Clin Oncol Off J Am Soc Clin Oncol. 2010;28(12):2085-2093. doi:10.1200/JCO.2009.25.1900

74. Ogura M, Tobinai K, Hatake K, et al. Phase I study of inotuzumab ozogamicin (CMC-544) in Japanese patients with follicular lymphoma pretreated with rituximab-based therapy. Cancer Sci. 2010;101(8):1840-1845. doi:10.1111/j.1349-7006.2010.01601.x

75. Kebriaei P, Cutler C, de Lima M, et al. Management of important adverse events associated with inotuzumab ozogamicin: expert panel review. Bone Marrow Transplant. 2018;53(4):449-456. doi:10.1038/s41409-017-0019-y

76. Hamadani M, Radford J, Carlo-Stella C, et al. Final results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma. Blood. 2021;137(19):2634-2645. doi:10.1182/blood.2020007512

77. Salles G, Gopal AK, Minnema MC, et al. Phase 2 Study of Daratumumab in Relapsed/Refractory Mantle-Cell Lymphoma, Diffuse Large B-Cell Lymphoma, and Follicular Lymphoma. Clin Lymphoma Myeloma Leuk. 2019;19(5):275-284. doi:10.1016/j.clml.2018.12.013

78. Fanale M, Assouline S, Kuruvilla J, et al. Phase IA/II, multicentre, open-label study of the CD40 antagonistic monoclonal antibody lucatumumab in adult patients with advanced non-Hodgkin or Hodgkin lymphoma. Br J Haematol. 2014;164(2):258-265. doi:10.1111/bjh.12630

79. Czuczman MS, Thall A, Witzig TE, et al. Phase I/II study of galiximab, an anti-CD80 antibody, for relapsed or refractory follicular lymphoma. J Clin Oncol Off J Am Soc Clin Oncol. 2005;23(19):4390-4398. doi:10.1200/JCO.2005.09.018

80. Armand P, Janssens A, Gritti G, et al. Efficacy and safety results from CheckMate 140, a phase 2 study of nivolumab for relapsed/refractory follicular lymphoma. Blood. 2021;137(5):637-645. doi:10.1182/blood.2019004753

81. Press OW, Unger JM, Braziel RM, et al. Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: five-year follow-up of Southwest Oncology Group Protocol S9911. J Clin Oncol Off J Am Soc Clin Oncol. 2006;24(25):4143-4149. doi:10.1200/JCO.2006.05.8198

82. Leonard JP, Coleman M, Kostakoglu L, et al. Abbreviated chemotherapy with fludarabine followed by tositumomab and iodine I 131 tositumomab for untreated follicular lymphoma. J Clin Oncol Off J Am Soc Clin Oncol. 2005;23(24):5696-5704. doi:10.1200/JCO.2005.14.803

83. Press OW, Unger JM, Rimsza LM, et al. Phase III randomized intergroup trial of CHOP plus rituximab compared with CHOP chemotherapy plus (131)iodine-tositumomab for previously untreated follicular non-Hodgkin lymphoma: SWOG S0016. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(3):314-320. doi:10.1200/JCO.2012.42.4101

84. Nastoupil LJ, Chin CK, Westin JR, et al. Safety and activity of pembrolizumab in combination with rituximab in relapsed or refractory follicular lymphoma. Blood Adv. 2022;6(4):1143-1151. doi:10.1182/bloodadvances.2021006240

85. Leonard JP, Schuster SJ, Emmanouilides C, et al. Durable complete responses from therapy with combined epratuzumab and rituximab: final results from an international multicenter, phase 2 study in recurrent, indolent, non-Hodgkin lymphoma. Cancer. 2008;113(10):2714-2723. doi:10.1002/cncr.23890

86. Grant BW, Jung SH, Johnson JL, et al. A phase 2 trial of extended induction epratuzumab and rituximab for previously untreated follicular lymphoma: CALGB 50701. Cancer. 2013;119(21):3797-3804. doi:10.1002/cncr.28299

87. Morschhauser F, Flinn IW, Advani R, et al. Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS). Lancet Haematol. 2019;6(5):e254-e265. doi:10.1016/S2352-3026(19)30026-2

88. Diefenbach C, Kahl BS, McMillan A, et al. Polatuzumab vedotin plus obinutuzumab and lenalidomide in patients with relapsed or refractory follicular lymphoma: a cohort of a multicentre, single-arm, phase 1b/2 study. Lancet Haematol. 2021;8(12):e891-e901. doi:10.1016/S2352-3026(21)00311-2

89. Hutchings M, Mous R, Clausen MR, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. Lancet Lond Engl. 2021;398(10306):1157-1169. doi:10.1016/S0140-6736(21)00889-8

90. Bannerji R, Arnason JE, Advani RH, et al. Odronextamab, a human CD20×CD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial. Lancet Haematol. 2022;9(5):e327-e339. doi:10.1016/S2352-3026(22)00072-2

91. Hutchings M, Morschhauser F, Iacoboni G, et al. Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell-Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial. J Clin Oncol Off J Am Soc Clin Oncol. 2021;39(18):1959-1970. doi:10.1200/JCO.20.03175

92. Subklewe M. BiTEs better than CAR T cells. Blood Adv. 2021;5(2):607-612. doi:10.1182/bloodadvances.2020001792

93. Tapia-Galisteo A, Compte M, Álvarez-Vallina L, Sanz L. When three is not a crowd: trispecific antibodies for enhanced cancer immunotherapy. Theranostics. 2023;13(3):1028-1041. doi:10.7150/thno.81494

94. Wu L, Seung E, Xu L, et al. Trispecific antibodies enhance the therapeutic efficacy of tumor-directed T cells through T cell receptor co-stimulation. Nat Cancer. 2020;1(1):86-98. doi:10.1038/s43018-019-0004-z

95. Yao Y, Hu Y, Wang F. Trispecific antibodies for cancer immunotherapy. Immunology. 2023;169(4):389-399. doi:10.1111/imm.13636

96. Fayad L, Offner F, Smith MR, et al. Safety and clinical activity of a combination therapy comprising two antibody-based targeting agents for the treatment of non-Hodgkin lymphoma: results of a phase I/II study evaluating the immunoconjugate inotuzumab ozogamicin with rituximab. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(5):573-583. doi:10.1200/JCO.2012.42.7211

97. Kolstad A, Illidge T, Bolstad N, et al. Phase 1/2a study of 177Lu-lilotomab satetraxetan in relapsed/refractory indolent non-Hodgkin lymphoma. Blood Adv. 2020;4(17):4091-4101. doi:10.1182/bloodadvances.2020002583

98. Palomba ML, Till BG, Park SI, et al. Combination of Atezolizumab and Obinutuzumab in Patients with Relapsed/Refractory Follicular Lymphoma and Diffuse Large B-Cell Lymphoma: Results from a Phase 1b Study. Clin Lymphoma Myeloma Leuk. 2022;22(7):e443-e451. doi:10.1016/j.clml.2021.12.010

99. Morschhauser F, Ghosh N, Lossos IS, et al. Obinutuzumab-atezolizumab-lenalidomide for the treatment of patients with relapsed/refractory

follicular lymphoma: final analysis of a Phase Ib/II trial. Blood Cancer J. 2021;11(8):147. doi:10.1038/s41408-021-00539-8

100. Czuczman MS, Hess G, Gadeberg OV, et al. Chemoimmunotherapy with ofatumumab in combination with CHOP in previously untreated follicular lymphoma. Br J Haematol. 2012;157(4):438-445. doi:10.1111/j.1365-2141.2012.09086.x

101. Westin JR, Chu F, Zhang M, et al. Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. Lancet Oncol. 2014;15(1):69-77. doi:10.1016/S1470-2045(13)70551-5

102. Czuczman MS, Leonard JP, Jung S, et al. Phase II trial of galiximab (anti-CD80 monoclonal antibody) plus rituximab (CALGB 50402): Follicular Lymphoma International Prognostic Index (FLIPI) score is predictive of upfront immunotherapy responsiveness. Ann Oncol Off J Eur Soc Med Oncol. 2012;23(9):2356-2362. doi:10.1093/annonc/mdr620

Figure Legends

Table 1. Published clinical trials assessing novel monoclonal antibodies in the treatment of follicular lymphoma:

Author, Year	Trial #	Phase	Disease Status	Experimental Agent	Control Agent	Progression Free Survival (PFS)	Complete Response Rate (CRR)	Objective Response Rate (ORR)
Hutchings et. al, 2021 [91]	NCT03075696	I	R/R	Glofitamab †	N/A	N/A	36.8%	53.8%
Bannerji et. al, 2022 [90]	NCT02290951	I	R/R	Odronextamab	N/A	N/A	72%	91%
Advani et. al, 2010 [73]	N/A	I	R/R	Inotuzumab Ozogamicin	N/A	10.4 months	N/A	68%
Ogura et. al, 2010 [74]	NCT00717925	I	Rituximab pretreated	Inotuzumab Ozogamicin	N/A	N/A	54%	85%
Tobinai et. al, 2011 [70]	N/A	I	Relapsed	LY2469298	N/A	N/A	30%	50%
Armand et. al, 2021 [80]	NCT02038946	I	R/R	Nivolumab	N/A	2.2 months	N/A	4%
Hamadani et. al, 2021 [76]	NCT02669017	I	R/R	Loncastuximab Tesirine	N/A	N/A	64.3%	78.6%
Huntchings et. al, 2021 [89]	NCT03625037	I/II	R/R	Epcoritamab	N/A	N/A	50%	90%
Hagenbeek et. al, 2008 [66]	NCT00092274	I/II	R/R	Ofatumumab	N/A	N/A	N/A	20% – 63%
Morschhauser et. al, 2009 [68]	NCT00285428	I/II	R/R	Veltuzumab	N/A	N/A	27%	44%
Morschhauser et. al, 2010 [69]	BO18418	I/II	R/R	Ocrelizumab	N/A	11.4 months	N/A	38%
Leonard et. al, 2003 [72]	N/A	I/II	R/R	Epratuzumab	N/A	86.6 weeks	N/A	24%
Fayad et. al, 2013 [96]	N/A	I/II	R/R	Inotuzumab Ozogamicin + R	N/A	2-years: 68%	N/A	87%
Czuczman et. al, 2005 [79]	N/A	I/II	R/R	Galiximab	N/A	N/A	6%	11%
Ganjoo et. al, 2015 [71]	NCT00354926	I/II	Previously treated	Ocaratuzumab	N/A	38.3 weeks	8%	30%
Kolstad et. al, 2020 [97]	NCT01796171	I/IIA	R/R	177-Lu-lilotomab Satetraxetan	N/A	N/A	N/A	65%
Fanale et. al, 2014 [78]	NCT00670592	IA/II	R/R	Lucatumumab	N/A	N/A	4.8 %	33.3%
Palomba et. al, 2022 [98]	NCT02220842	IB	R/R	Flizumab + Obinutuzumab	N/A	9 months	23%	54%
Diefenbach et. al, 2021 [88]	NCT02600897	IB/II	R/R	Polatuzumab-Vedotin + Obinutuzumab + Lenalidomide	N/A	N/A	63%	76%
Morschhauser et. al, 2021 [99]	NCT02631577	IB/II	R/R	Atezolizumab + Obinutuzumab + Lenalidomide	N/A	36-months: 68.4%	N/A	N/A
Morschhauser et. al, 2019 [87]	NCT01691898	II	R/R*	Polatuzumab-Vedotin + R**	Pinatuzumab-Vedotin + R	N/A	45%Δ	70%Δ
Czuczman et. al, 2012 [100]	NCT00494780	II	Untreated	Ofatumumab + CHOP ΔΔ	N/A	N/A	62%	90% – 100%
Rosenbaum et. al, 2019 [65]	NCT01190449	II	Untreated	Ofatumumab	N/A	1.9 years	9%	84%
Leonard et. al, 2008 [85]	N/A	II	R/R	Epratuzumab + R	N/A	10 months	24%	54%
Grant et. al, 2013 [86]	NCT00553501	II	Untreated	Epratuzumab + R	N/A	3.5 years	42.4%	88.2%
Westin et. al, 2014 [101]	NCT00904722	II	Relapsed Rituximab-Sensitive	Pidilizumab + R	N/A	18.8 months	52%	66%
Press et.al, 2006 [81]	S9911	II	Untreated	CHOP + Tositumomab/I-131 Tositumomab	N/A	5-years: 67%	69%	91%
Leonard et.al, 2005 [82]	N/A	II	Untreated	Fludarabine + Tositumomab/I-Tositumomab‡	N/A	N/A	86%	100%
Czuczman et. al, 2012 [102]	NCT00117975	II	Untreated	Galiximab + R	N/A	2.9 years	47.6%	72.1%
Salles et. al, 2019 [77]	NCT02413489	II	Relapsed	Daratumumab	N/A	N/A	N/A	12.5%
Nastoupil et.al, 2022 [84]	NCT02446457	II	R/R	Pembrolizumab + R	N/A	12.6 months	23%	93%
Czuczman et. al, 2012 [67]	NCT00394836	III	Rituximab Refractory	Ofatumumab	N/A	5.8 months	N/A	22%
Press et. al, 2013 [83]	S0016	III	Untreated	CHOP + I-Tositumomab‡	CHOP + R	2-years: 80%Δ	45%Δ	93%Δ

* Relapsed/Refractory
** Rituximab
Δ PFS, CR, ORR are those of the experimental group.
ΔΔ CHOP is Cyclophosphamide, Doxorubicin, Prednisone and Vincristine.
† Glofitamab was pre-phased with Obinutuzumab
‡ I-Tositumomab is 131 Iodine Tositumomab

Table 2. Ongoing clinical trials investigating novel monoclonal antibodies in follicular lymphoma.

Trial #	Experimental Agent	Control Agent	Disease Status	Phase	Estimated Completion Date
NCT03150329	Pembrolizumab + Vorinostat	N/A	R/R	I	June 18, 2023
NCT03401853	Pembrolizumab + Rituximab	Pembrolizumab + Obinutuzumab	R/R	II	July 30, 2024
NCT03498612	Pembrolizumab	N/A	Untreated	II	September 1, 2023
NCT03361852	Pembrolizumab and NeoVax	NeoVax	N/A	I	March 14, 2026
NCT03035331	Pembrolizumab, + Dendritic Cell Therapy + Cryosurgery	N/A	N/A	I/II	July 1, 2023
NCT05788081	Nivolumab + BMS-986369 + Rituximab	BMS-986369 + Rituximab	Newly Diagnosed	II	June 1, 2027
NCT03884998	Nivolumab + Copanlisib	N/A	Transformed	I	December 16, 2023
NCT05169658	Obinutuzumab + Polatuzumab Vedotin + Mosunetuzumab	Mosunetuzumab	Untreated	II	August 1, 2024
NCT05672251	Oncastuximab Tesirine + Mosunetuzumab	N/A	R/R	II	December 28, 2024
NCT05783609	Epcoritamab + Rituximab	N/A	Untreated	II	February 22, 2029
NCT04663347	Epcoritamab	Tested in 8 different arms with 8 different agents	Both Untreated and R/R	IB/II	November 30, 2024
NCT03625037	Epcoritamab	N/A	N/A	I/II	April, 2029
NCT03075696	Glofitamab	N/A	Obinutuzumab Treated	I/II	August 28, 2025
NCT02290951	Odronextamab	N/A	N/A	I	December 2, 2025
NCT05152459	Tazemetostat + Umbralisib + Ublituximab	N/A	R/R	I/II	December 15, 2024
NCT05783596	Obinutuzumab + Glofitamab	N/A	Untreated	II	January 8, 2029
NCT04834024	MIL62 + Lenalidomide	Lenalidomide	Rituximab Refractory	III	March 2025
NCT04587687	Brentuximab Vedotin + Bendamustine	N/A	R/R	II	May 1, 2024
NCT02568553	Blinatumomab + Lenalidomide	N/A	R/R	I	December 31, 2023
NCT02520791	MEDI-570	N/A	R/R	I	December 31,2023
NCT03410901	Anti-OX40	N/A	N/A	I	October 10, 2023
NCT01796171	Lilotomab	N/A	R/R	II	November 2022
NCT04594642	TNB-486	N/A	R/R	I	May 2024
NCT05611853	BN-301	N/A	N/A	I/II	December 30, 2024
NCT03424603	STRO-001	N/A	Advanced	I	November 2023
NCT04903197	Ianalumab (VAY736)	N/A	N/A	I/IB	June 30, 2027
NCT05365659	IKS03	N/A	Advanced	I	July 2027
NCT04358458	GEN3009	N/A	R/R	I/2A	September 4, 2025
NCT05025800	ALX148	N/A	R/R	I/II	March 10, 2026
NCT04806035	TG-1801	TG-1801 + Ublituximab	N/A	IB	December 2023
NCT05003141	PSB202	N/A	R/R	IA/IB	January 2024

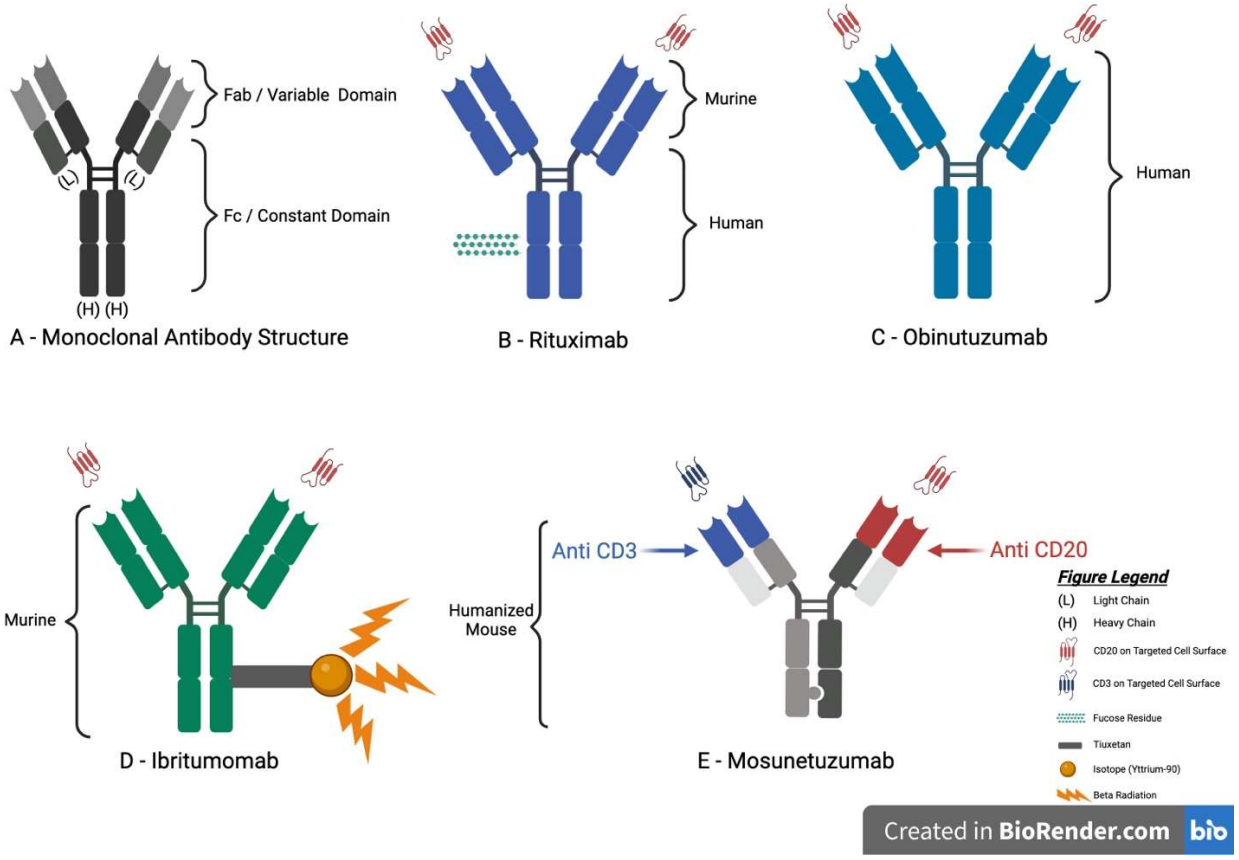

Figure 1. Structure of the approved monoclonal antibodies in follicular lymphoma. a) general structure of a monoclonal antibody, with the upper variable domain (Fab) and lower constant domain (Fc) as well as two heavy chains (H) and two light chains (L); b) structure of Rituximab with fucose residues attached; c) structure of Obinutuzumab with absence of the fucose residues which increases its affinity to bind effector cells; d) structure of Ibritumomab, covalently linked to the chelator tiuxetan, to which is further added a radioactive isotope, (yttrium-90), which emits beta radiation and induces cellular damage; e) structure of Mosunetuzumab showing one Fab segment directed towards CD20, and the other Fab segment directed towards CD3.