Current and emerging monoclonal antibodies, antibody-drug conjugates, and bispecific antibodies in treatment of lymphoma

Suheil Albert Atallah-Yunes a, *, Michael J. Robertson b

a Division of Hematology and Medical Oncology – Melvin and Bren Simon Cancer Center, Indiana University School of Medicine, Indianapolis, IN, USA
b Lymphoma Program, Division of Hematology and Medical Oncology – Melvin and Bren Simon Cancer Center, Indiana University School of Medicine, Indianapolis, IN, USA

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ABSTRACT

The improvement in outcomes seen with the introduction of rituximab, a CD20 monoclonal antibody in combination with chemotherapy or as a single agent in the treatment of indolent non-Hodgkin lymphomas has paved the way for development of various forms of monoclonal antibodies that act in different ways against non-Hodgkin lymphoma tumor cells. These could directly target a single surface antigen resulting in various ways of tumor cells toxicity and killing. Other forms of monoclonal antibodies include antibody-drug conjugates and bispecific antibodies. The role of therapeutic monoclonal antibodies in the treatment of lymphoma will be reviewed, highlighting their mode of action, clinical efficacy, and side effects.

1. Introduction

The discovery of monoclonal antibodies (MAbs) and the advancement in immunotherapy have revolutionized the treatment of indolent and aggressive non-Hodgkin lymphomas (NHLs). For many years, chemotherapy had been the standard treatment for aggressive NHL failing to cure more than 50% of patients [1, 2]. The improvement in outcomes seen with the introduction of rituximab, a CD20 MAb in combination with chemotherapy or as a single agent in indolent NHLs has paved the way for various MAbs that act in different ways against NHL tumor cells. These could directly target a single surface antigen resulting in direct toxicity while also binding to other effector cells via its Fc portion resulting in antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent phagocytosis (ADP), and complement-mediated killing of tumor cells [2, 3]. Antibody-drug conjugates (ADC) are comprised of MAbs linked to cytotoxic drugs that are internalized into the tumor cell after binding of the MAb to a specific surface antigen [4]. More recently, bispecific antibodies have been implemented, that target effector cells, such as T-cells and natural killer (NK)-cells, towards tumor cells [5].

2. Monoclonal antibodies

2.1. Rituximab

Rituximab is the first type 1 MAb to receive FDA approval for the frontline treatment of NHL. Rituximab recognizes the CD20 surface antigen which is expressed by about 95% of lymphoma B-cells and virtually all normal mature B-cells, making it an attractive therapeutic target. When rituximab binds to its target, it stabilizes the CD20 receptors on the hydrophobic membrane of the cell resulting in a more potent complement-mediated killing of the B-cell but also an increased cellular signaling that accelerates apoptosis. The Fc portion of rituximab can bind to Fc receptors on NK cells and macrophages to promote ADCC and ADP, respectively [2, 3].

In 1997, rituximab received its first approval by the FDA for the treatment of indolent NHLs based on the phase II trial by McLaughlin et al. in relapsed indolent NHLs [6]. This came following the in vitro and in vivo preclinical studies by Reff et al. and the phase 1 study by Maloney et al which not only demonstrated activity of rituximab against NHL cells but also that higher rituximab MAb concentration is associated with more activity against NHL cells which was maintained after multiple doses of rituximab [1, 7]. The pivotal phase 2 study by McLaughlin in 166 patients with relapsed low grade NHL demonstrated...
48% overall response rate (ORR), 6% had complete remission (CR) and 42% had partial remission (PR) after 4 doses of weekly 375 rituximab [6]. More recently, late phase trials reported excellent results with single agent rituximab in untreated follicular lymphoma (FL) patients, hence it is commonly used as first-line induction therapy especially in patients with low burden FL disease [8]. Phase III trials in FL patients showed that induction with rituximab plus chemotherapy is superior to chemotherapy alone (CVp, CHP, CHOp) in terms of CR, progression free survival (PFS) and overall survival (OS) [3]. Most of the guidance in the frontline management of FL patients who have indications for treatment are based on data extrapolated from several phase III pivotal studies: PRIMA (NCT00140582), StiL (NCT00991211), BRIGHT (NCT00877006) and GALLIUM (NCT01332968) which included patients with FL and other indolent forms of NHLs [9-12]. Bendamustine and rituximab (BR) is preferred over R-CHOP in the frontline chemoimmunotherapy treatment of FL given the superior PFS and tolerability seen with BR compared to R-CHOP with no differences in OS [10]. The PRIMA study showed that maintenance rituximab substantially improved PFS but did not improve OS after frontline R-CHOP or R-CVP [11]. The role of maintenance rituximab after treatment with BR is a subject of controversy, as data from prospective randomized clinical trials have not shown clear benefit of maintenance rituximab in this setting.

Marginal Zone Lymphoma is another indolent or low-grade NHL. A meta-analysis of 13 studies with 237 patients evaluated the efficacy and safety of rituximab treatment in marginal zone lymphoma, showing an ORR of 81% and a CR rate of 50% [2]. Other uses for rituximab with positive outcomes include posttransplant lymphoproliferative disorders (PTLD) and Waldenström’s disease.

Subsequently, rituximab received its approval by the FDA in 2006 for the frontline treatment of DLBCL in combination with CHOP or CHOP-like therapy based on the pivotal phase 3 trial by Coiffier et al. (LNH-98.5 trial) which demonstrated a superior 10 year OS in the R-CHOP group over the CHOP group (43.5% vs 27.6% respectively) [13]. Habermann et al. confirmed a superior failure free survival (FFS) in patients who received rituximab with CHOP during induction or maintenance after CHOP compared to CHOP alone in patients > 60 years old [14]. Better outcomes are seen in young patients who have lower IPI scores. The phase III trial by Pfunderschuh et al. (NCT00064116) reported a 93% 3 years OS in those who received rituximab + CHOP like therapy compared to 84% in those who received CHOP like therapy alone. All patients were below the age of 60 and had low risk IPI score [15]. Subanalysis of the study by Habermann et al. demonstrated no improvement in OS when rituximab was given as maintenance therapy in DLBCL patients who received rituximab with CHOP during induction therapy [14]. Rituximab is also used with chemotherapy for salvage treatment of refractory/relapsed (R/R) DLBCL.

In mantle cell lymphoma (MCL), rituximab is incorporated with chemotherapy at the frontline with improvement in OS [16]. It is also given as maintenance treatment after induction with chemotherpay and after autologous stem cell transplant (ASCT) (NCT00921414) given the improved OS seen in phase III trials in this setting [16-18].

Infusion-related reactions are the most common side effects of rituximab, mostly occurring during the first infusion. Most of the reactions are mild but severe reactions such as hypotension and bronchospasm could occur (12%). Hepatitis B reactivation has been reported and thus Hepatitis B immunization status should be checked in all individuals before starting rituximab. Less commonly, cytopenia and infections could occur. Hypogammaglobulinemia may occur after rituximab-based therapy and can be treated with intravenous immunoglobulins (IVIg) if recurrent infections are reported [3]. Responses to vaccines may be impaired with rituximab due to B-cell depletion. Levy et al. [19] evaluated the response to COVID-19 vaccine in 126 lymphoma patients who received rituximab by measuring antibodies to viral spike proteins. The last dose of rituximab varied from days to 18 years prior the vaccine. 55% of patients developed antibodies however none of the 33 patients who received rituximab within the 6 months prior to the vaccine developed antibodies. Results showed that patients who received rituximab within 12 months prior to vaccine administration are less likely to develop antibodies. 10 of the 15 patients who received the vaccine prior to initiation of rituximab developed antibodies [19]. The optimal timing of receiving COVID-19 vaccination to mount a response after finishing rituximab therapy is unknown yet. It is also still unclear how rituximab could affect the T-cell response. Despite these findings and given the higher risk of severe COVID-19 infection in lymphoma patients due to cancer and treatments including rituximab, it is still recommended to administer the COVID-19 vaccine to these patients however prior to initiation of rituximab if possible since come patients were able to generate antibodies in this setting and closer to the end of the rituximab cycle if rituximab was already started. Delaying rituximab treatment until after COVID-19 vaccination may be appropriate in settings in which rituximab has no impact on OS such as maintenance therapy in indolent lymphomas.

2.2. Ofatumumab

Ofatumumab is a fully human IgG1 monoclonal antibody that binds to different epitope of CD20 than that recognized by rituximab. Compared to rituximab, ofatumumab mediates more potent ADCC and complement-dependent cytotoxicity against CD20+ lymphoma cells in vitro. Table 1 shows the differences between various CD20 MABs. Ofatumumab is approved by the FDA for treatment of relapsed or refractory chronic lymphocytic leukemia (CLL). Ofatumumab has also been shown to have activity in FL and DLBCL. However, ofatumumab failed to show improvement in outcomes (ORR, CR, OS and PFS) over rituximab with more adverse events in those who received ofatumumab [20]. In a phase 3 trial (NCT01077518), the addition of ofatumumab to bendamustine in NHL patients refractory to rituximab, failed to improve OS and PFS [21].

2.3. Obinutuzumab

Obinutuzumab is a type 2 CD20 MAbs that differs from type 1 MABs such as rituximab by having less ability to concentrate C20 receptors in cell membrane lipids resulting in less complement-mediated killing. However, obinutuzumab has a modified Fc portion that induces more potent ADCC and ADP than type 1 MABs [22]. Among the NHLs, obinutuzumab is mostly implemented in the treatment of FL. After its clinical activity was established in early phase trials, the phase 3 GADOLIN trial (NCT01059630) in FL patients refractory to rituximab or relapsed within 6 months of rituximab demonstrated 43% less disease worsening and death in those who received obinutuzumab plus Bendamustine than Bendamustine alone which led to the approval of this combination regimen in the induction treatment of FL patients who progressed or relapsed within 6 months of rituximab [23]. Induction is followed by maintenance obinutuzumab as it was done in the GADOLIN trial [23].

The phase 3 Gallium study (NCT01332968) compared obinutuzumab plus chemotherapy vs rituximab plus chemotherapy in untreated FL patient and showed 32% lower risk of disease worsening of death in patients who received obinutuzumab which led to the approval of

| Table 1 | Comparison between CD20 monoclonal antibodies. |
|---------|--------------------------------------------|
| Monoclonal antibody | Type  | Structure | CDC | ADCC | Direct cell death |
| Rituximab     | I     | Chimeric  | +   | ++  | +             |
| Ofatumumab    | I     | Humanized | ++  | ++++| ++++ +++++  |
| Obinutuzumab  | II    | Human     | +   | ++  | +             |

Abbreviations CDC: complement dependent cytotoxicity; ADCC: antibody dependent cell mediated cytotoxicity.
obinutuzumab plus chemotherapy at the frontline treatment of untreated FL patients [12]. Despite the superior outcomes of obinutuzumab to rituximab in these studies, this was not translated into a superior OS yet. In DLBCL patients, obinutuzumab did not have superior outcomes to rituximab as was seen in the GOYA trial (NCT01287741) [24]. The side effects of obinutuzumab are similar to rituximab however tend to occur more frequently with obinutuzumab. Strategies that are being implemented in early studies include combining obinutuzumab with immunomodulatory agents, ADCS and other forms on immunotherapy [22].

2.4. Ublituximab

Ublituximab is a type 1 IgG1 chimeric MAb that targets CD20 but is engineered to have more potent ADCD than rituximab. Ublituximab seems to have high activity in indolent NHL with impressive results seen in marginal zone lymphoma and CLL/SLL and is being studied in combination with other therapeutic agents such PI3K-δ and cascin kinase-1ε inhibitor mainly in indolent NHLs [25].

2.5. Tafasitamab

The emergence of resistance to CD20 MABs has led to the development of other MABs targeting different antigens on the malignant B cells. Tafasitamab targets CD19 which is expressed on both immature and mature B cells. Tafasitamab has a modified Fc portion which enhances ADCD and ADP activity of effector cells against NHL tumor cells [26, 27].

The clinical activity of tafasitamab was demonstrated in phase 1 studies of refractory CLL/SLL. In NHL, Phase 2 studies showed impressive outcomes in R/R DLBCL patients ineligible for salvage therapy and ASCT. In a phase II trial of tafasitamab (NCT01685008) in 92 patients with R/R NHL (35 DLBCL, 34 FL, 12 MCL, and 11 other indolent forms of NHL), ORR was 26%, 29% and 27% in DLBCL, FL and other indolent forms of NHL patients respectively. At long-term follow-up (< 4 years), median PFS was 2.7 months in DLBCL patients; 12-month PFS was 34% and the median duration of response (DOR) was 20.1 months. It is noted that none of the patients with MCL responded [28, 29].

Ongoing phase 2 studies are exploring regimens that include tafasitamab in combination with other agents, including the immunomodulatory drug lenalidomide, which led to enhanced NK-cell activity when combined with tafasitamab [27]. Updated results from the ongoing phase 2 L-MIND trial (NCT02399085), showed 58.8% ORR and 41.3% CR with a median PFS of 16.2 months and median survival of 31.6 months in 81 patients with R/R DLBCL ineligible for ASCT who received tafasitamab plus lenalidomide. Median DOR was not reached for those with CR while it was 5.6 months for those with PR [30]. This led to the accelerated approval of tafasitamab in combination with lenalidomide by the FDA in August 2020 for treatment of R/R DLBCL. Other studies comparing tafasitamab to other regimens such as BR are ongoing. Future studies may also focus on combining tafasitamab with chemotherapy in the frontline treatment of DLBCL provided tolerability is confirmed in early studies [27]. In general, tafasitamab is well tolerated with the most common adverse events being cytopenias that were more profound when used in combination with lenalidomide [26, 27].

2.6. Epratuzumab

Epratuzumab is a humanized MAB that targets CD22. CD22 is a transmembrane sialoglycoprotein that plays a role in cell functioning and proliferation. Its expression is mainly limited to B-lymphocytes and its highly expressed in marginal zone lymphoma, FL and MCL. Epratuzumab phosphorylates CD22 affecting BCR signaling and induces ADCD [31]. In a phase 1 study (NCT00553501) in patients with untreated FL, induction with epratuzumab and rituximab led to an ORR and CR of 88% and 42% respectively with a median PFS of 3.5 years. In phase 2 study in patients with R/R NHL, epratuzumab + rituximab led to ORR and CR/CRu of 64% and 24% respectively in R/R FL and 47% and 33% respectively in R/R DLBCL. 33% of patients with marginal zone lymphoma responded including 1 CR [32]. In a phase 2 study (NCT00301821) of epratuzumab + rituximab in untreated DLBCL patients resulted in ORR of 96%, CR of 75% and 3 years OS and PFS of 80% and 76% respectively.

3. Antibody-drug conjugates (ADC)

An ADC is a compound of antibody linked to a cytotoxic agent (payload) by a chemical linker. After the antibody binds to the target antigen on tumor cells, the complex gets internalized into the cell and the linker gets degraded releasing the cytotoxic agent [4]. When used in the treatment of lymphoma, the antibody by itself may have ADCD and complement-mediated killing effects against neoplastic B-cells. However, the modest B-cell depletion caused by the antibody may become more prolonged and sustained when linked to a cytotoxic agent by the chemical linker forming the ADC complex. Thus, an ideal ADC designed to treat lymphoma would include: 1) a MAb that targets antigens specifically expressed on target cancer cells and not or minimally expressed on normal tissue 2) a linker that is chemically stable in systemic circulation and only degraded intracellularly in the target cell by proteases or environmental changes such as pH reduction 3) a payload that is stable and a powerful cytotoxic agent against lymphoma cells. Payloads interfere with cellular mechanisms that eventually cause apoptosis and death of the lymphoma cell [33, 34]. Examples of payloads implemented in ADCs include auristatins such as monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF), derivatives of maytansinoids such as DM1 and DM4 and derivatives of calicheamycins such as N-ace-tyl-c-calicheamicin dimethyl hydrizade (Calich-DMH). Auristatins and maytansinoids cause apoptosis by disrupting the microtubules while calicheamycins cause apoptosis by DNA intercalation [35, 34].

3.1. Brentuximab vedotin

Brentuximab vedotin is an ADC that targets the CD30 antigen and delivers the cytotoxic moiety MMAE [35]. Brentuximab vedotin is used with chemotherapy in the first line treatment of classical Hodgkin lymphoma (cHL) and systemic and cutaneous T-cell lymphomas that express CD30. Several NHL subtypes were also found to express CD30 including: DLBCL (Up to 25%), primary mediastinal DLBCL, marginal zone lymphoma and PTLD where modest activity of brentuximab vedotin was seen [35], thus its use as monotherapy in NHL is mostly limited to the R/R setting or in patients who are unfit for chemotherapy. In cHL, brentuximab vedotin has gained FDA approval for treatment in different disease settings. Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine) is approved for treatment of previously untreated advanced stage cHL based on the phase 3 ECHELON-1 trial (NCT01712490) which randomized advanced stage cHL patients to either receive ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or brentuximab vedotin + AVD and demonstrated an improvement in PFS with brentuximab vedotin + AVD (82.1% vs 77.2%) with sub-analysis showing that those with IPI 4–7, stage IV disease, more than 1 extranodal involvement and young patients are likely to benefit the most [36]. However, given the only slight improvement in PFS and significant proportion of patients developing peripheral neuropathy and febrile neutropenia with the brentuximab vedotin regimen, choosing between AVBD and brentuximab vedotin + AVD is mainly personalized and dependent on toxicity profile such as risk of pulmonary toxicity with bleomycin.

Brentuximab vedotin monotherapy is approved by the FDA for treatment of R/R HL after ASCT or after using 2 prior lines of therapy. The pivotal phase 2 study by Younes et al. (NCT00848926) for brentuximab vedotin monotherapy in patients with classical HL who relapsed after ASCT resulted in CR and ORR of 34% and 75% respectively.
Polatuzumab vedotin is a compound of CD79b MAb linked to MMAE \cite{4, 27}. The CD79 is a heterodimeric signal transduction component of the B-cell receptor. The CD79b MAb in polatuzumab vedotin has a negative signaling effect and may lead to modest ADCC and complement-mediated killing on the NHL cell which becomes prolonged and more sustained when linked to MMAE \cite{48}. The use of CD79b ADCs such as polatuzumab vedotin, has been an attractive therapeutic strategy in NHL due to the expression of CD79 being almost exclusively limited to B-cells and most NHLs and also due to trafficking when combined with rituximab however significant adverse events including eye toxicity (25%) were seen and could explain the decreased interest in studying this drug \cite{55}. MT-3724 consists of CD20 MAb conjugated to irreversible ribosome inhibitor made form Shiga like toxin (SLT) A subunit and showed promising results in phase 1 studies that led to multiple ongoing phase 2 studies for this ADC in R/R DLBCL patients. Neuropathy is dose and duration dependent, it is recommended to hold polatuzumab in those who develop high grade neuropathy until improvement to grade 1 or total resolution with subsequent dose reduction \cite{4}.

3.3. Loncastuximab tesirine

Loncastuximab tesirine is an ADC comprising a humanized CD19 MAb conjugated to a pyrrolobenzodiazepine dimer (PBD) toxin. In the phase 1 dose expansion study (NCT02669017) of loncastuximab tesirine in 183 patients with R/R NHL ORR was 46% with a CR rate of 27% and a median DOR of 5.4 months. ORRs were 42%, 47%, and 79% in DLBCL, MCL and FL patients respectively. ORR was 42.3%, with 23.4% CR in the DLBCL cohort; the median DOR was not reached, and the PFS was only 2.8 months \cite{53}. The updated analysis of data from a phase 2 trial (NCT03589469) in 145 patients with R/R DLBCL reported an ORR of 48%, a CR rate of 24% and a median DOR of 10.3 months. ORR in patients with double- or triple -hit lymphoma was 33% (all CR). In those who failed prior CAR-T cell therapy, ORR was 46% \cite{54}. The most common adverse side effects reported with locastuximab tesirine are hematologic toxicities followed by liver toxicity, nausea and edema \cite{53, 54}.

3.4. Other ADCs

Coltuximab ravtansine is a CD19 directed ADC that has DM4 as a payload and resulted in modest activity in R/R NHL as monotherapy and when combined with rituximab however significant adverse events including eye toxicity (25%) were seen and could explain the decreased interest in studying this drug \cite{55}. MT-3724 consists of CD20 MAb conjugated to irreversible ribosome inhibitor made form Shiga like toxin (SLT) A subunit and showed promising results in phase 1 studies that led to multiple ongoing phase 2 studies for this ADC in R/R DLBCL patients (NCT02361346) (NCT03488251). Inotuzumab ozagamycin is a compound of CD22 MAb linked to a calicheamicin derivative payload and is approved for treatment of R/R B cell lineage acute lymphoblastic leukemia (B-ALL) however is increasingly being studied in first line treatment of B-ALL. In R/R NHL, inotuzumab ozagamycin led to an ORR of 68% and 15% in R/R FL and R/
4. Bispecific antibodies

Bispecific antibodies are antibodies that bind two distinct antigens linking effector cells (T cells or NK cells) to tumor cells. More than half of these are bispecific T cell engagers (BiTEs) that engage the CD3 invariant subunit of the T cell receptor complex, resulting in activation of cytotoxic T cells against tumors leading to tumor cell lysis. Most of the BiTEs undergoing development for B cell NHL link the CD3 antigen to CD19 (CD19 x CD3 BiTE) or CD20 (CD20 xCD3 BiTE).

Fc-free BiTEs allow more penetration to tumor tissue but have a rapid clearance due to small molecular size, hence requiring administration as a continuous intravenous infusion. IgG like BiTEs have full or modified Fc regions that have less affinity to Fc receptors. The lack of Fc receptor or its modification to have lower affinity to Fc receptors result in more specific T cell activation and less activation of other immune effector cells such as macrophages and NK cells. Overactivation of T cells could explain the most notable and concerning side effects of BiTE including cytokine-release syndrome (CRS) and neurotoxicity. Lymphopenia is common as CD19 and CD20 antigens are also expressed on normal B-cells but this can be compensated by administration of IVIg until restoration of the B-cell lineage. The other immune effector cell that received a focus in development of bispecific antibodies is the NK cell [5, 60].

4.1. CD19 x CD3 BiTE

Blinatumomab is the first CD19 xCD3 BiTE approved for clinical use, in the second line treatment of B-ALL. Early clinical trials showed impressive results with blinatumomab in patients with R/R B-cell NHL. In the phase 1 trial by Goebeler et al. (NCT00274742), ORR was 69% (37% CR + CRu and 31% PR) in 35 patients with NHL whom were able to tolerate the full escalation and maximum tolerable dose of blinatumomab 60 μg/m²/day. Responses were seen among all NHL types, FL (ORR, 80%), MCL (ORR, 71%), and DLBCL (ORR, 55%). For the entire group, median duration of response and OS were 404 days and 4.6 years respectively, those who received the maximum dose and responded had a median OS of 7.7 years with 6 patients being treatment free for more than 7 years. Patients treated with doses lower than 60 μg/m²/day had a median OS of 1.1 years [61].

A phase II trial (NCT01741792) of blinatumomab in heavily treated R/R DLBCL, ORR and CR were 43% and 19% respectively in 21 patients who were able to receive blinatumomab for at least one week at target dose or stopped treatment sooner due to disease progression [62]. In the phase 2 study of blinatumomab in 41 patients with DLBCL refractory to 1st line salvage chemotherapy, ORR and CR were 37% and 22% respectively indicating that blinatumomab may be a potential regimen with useful activity in bridging to ASCT/allogenic SCT in R/R DLBCL [63]. High grade CRS and neurotoxicity can occur with blinatumomab; up to 22% of patients developed grade 1–3 reversible neurotoxicity in the phase 1 trial. Hence dexamethasone should be administered prior to the first dose and with every dose escalation [5, 64]. Given the presence of other competitive agents with superior outcomes in the R/R DLBCL setting, most phase 3 trials of blinatumomab have been on hold. The short half-life of blinatumomab with the necessity of continuous infusion makes it inconvenient for many patients. Early studies with the strategy of combining blinatumomab with immune check point inhibitors and immune modulatory agents are ongoing [5, 64]. Other CD19 x CD3 BiTEs include MGD011 (duvortuxizumab) and AFM11, which were tested in phase 1 studies that were discontinued early due to high levels of neurotoxicity [5].

4.2. CD20 x CD3 BiTE

Mosenutuzumab is a CD20 xCD3 BiTE that demonstrated activity in R/R NHL with best ORR and CR of 34.9% and 19.4% respectively in patients with R/R aggressive NHL involved in a phase 1 dose escalating study of patients with R/R NHL (NCT02500407). Those with indolent NHL had better responses (ORR 66.2%, CR 48.5%) [65]. Ongoing focus now is on studying mosenutuzumab in combination with other immunotherapeutic agents. Glofitamab is another CD20 xCD3 BiTE that was tested in a phase 1 dose escalating study (NCT03075696) with and without obinutuzumab and resulted in 34.1% and 49.4% CR and ORR respectively in the subset of patients with R/R aggressive NHL. A current trial is studying glofitamab in combination with chemotherapy in untreated DLBCL [66]. Plomatamab [67], ecopritamab [68] and odronextamab / REGN 1979 [69] are another CD20 x CD3 BiTEs that showed promising results in early studies of patients with R/R DLBCL. REGN 1979 is a CD20 x CD3 BiTE was tested in a phase 1 study in R/R NHL patients and showed 100% ORR in 10 patient with R/R FL [5]. FBTA05 is a CD20 x CD3 BiTE - with a functional Fc region that also activates other immune effector cells (macrophages and NK-cells) and showed promising results in the pediatric patients [5].

4.3. Bispecific NK cell engagers

Bispecific NK cell engagers are bispecific Mabs that activate NK cells rather than T-cells. Several activating receptors on NK cells could act as a targets. The CD16A receptor can activate NK cells without costimulatory signals, leading to increased interferon-gamma production and destruction of tumor cells. AFM13 is a bispecific NK cell engager that targets that CD16A on NK cells and CD30 on NHL and Hodgkin lymphoma tumor cells. To increase activation of the NK cell and prevent the degradation of CD16A by metalloproteinases and disintegrin; several strategies are being implemented including: the addition of metalloproteinase inhibitors, targeting more than one receptor on the NK-cell and incorporating IL-15 making trispecific NK cell engagers [5].

5. Conclusion

Mabs in their various forms have improved treatment outcomes for patient with previously untreated and R/R lymphoma. The treatment landscape of lymphoma is evolving as the roles of current and emerging therapeutic Mabs, ADCs and bispecific antibodies are elucidated in ongoing and future studies.

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