Leukemia Research Reports 17 (2022) 100319

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

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

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ARTICLE INFO

Keywords:
Lymphoma
Immunotherapy
Monoclonal antibodies
Antibody drug conjugates
Bispecific antibodies

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 el 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

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https://doi.org/10.1016/j.lrr.2022.100319
Received 27 July 2021; Received in revised form 19 April 2022; Accepted 27 April 2022
Available online 28 April 2022
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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 Waldenstrom'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 $>$ or $=$60 years old [14]. Better outcomes are seen in young patients who have lower IPI scores. The phase III trial by Pfreundschuh 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 chemoimmunotherapy 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 MAb 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	++	++	+
Obinutuzumab	II	Humanized	+	++++	++++
Ofatumumab	I	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 ADCC 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 casein kinase-1ε inhibitor mainly in indolent NHLs [25].

2.5. Tafasitamab

The emergence of resistance to CD20 MAbs have 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 ADCC 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 tafastitamab 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 tolerabilty 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 siaglycoprotein that plays a role in cell functioning and proliferation. Its expression is mainly limited to B-lymphocytes and itis highly expressed in marginal zone lymphoma, FL and MCL. Epratuzumab phosphorylates CD22 affecting BCR signaling and induces ADCC [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 + CHOP 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 ADCC 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 mytansinoids such as DM1 and DM4 and derivatives of calicheamycin such as N-acetyl-c-calicheamicin dimethyl hydrazide (Calich-DMH). Auristatins and mytansinoids cause apoptosis by disrupting the microtubules while calicheamycins cause apoptosis by DNA intercalation [33, 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 animprovement in PFS with brentuximab vedotin + AVD (82.1% vs 77.2%) with subanalysis 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 ABVD 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. Median PFS was 9.3 months while median DOR was 20.3 months in those who achieved CR. In 5 years, estimated PFS and OS were 22% and 41% respectively [37, 38]. In patients who have R/R cHL and relapsed after ASCT or are ineligible for ASCT, pembrolizumab may be preferred over brentuximab vedotin based on the superior PFS with the former drug that was seen in the KEYNOTE-204 phase 3 trial (NCT02684292) comparing both single agents in this setting [39]. Brentuximab vedotin is also approved as a maintenance therapy after ASCT in patients with high risk cHL (primary refractory or relapsed with 12 months of frontline therapy or more than one extranodal organ involvement) based on the phase 3 AETHERA trial (NCT01100502) which randomized high risk patients to receive either brentuximab vedotin q 3 weeks and up to 16 cycles or placebo within 30 to 45 days of ASCT. PFS for the brentuximab vedotin and placebo groups were 42.9% and 24.1 months respectively [40] with long term follow up showing a 5-year PFS of 59% and 41% with brentuximab vedotin and placebo respectively [41].

Brentuximab vedotin has shown promising results in phase 1 and 2 trials when combined with other therapeutic agents such as with salvage platinum based regimens prior to ASCT [42]. A promising bridging regimen includes bendamustine + brentuximab vedotin which showed an ORR and CR of 93% and 74% respectively [43] in a phase 1/2 study (NCT01874054). There is an interest in studying bendamustine + brentuximab vedotin at the frontline setting especially in patients with comorbidities and cardiac disease. Additionally, brentuximab vedotin has been evaluated in combination with AVD in early stage cHL which showed promising CR rates [44, 45] however the significant increase in toxicities resulting from the addition of brentuximab vedotin may suggest that this regimen may be further studied in patients with unfavorable early stage cHL and is less appealing in favorable disease (NCT01868451) (NCT01534078).

In order to improve the outcomes seen with immunotherapy alone in patients with R/R cHL, brentuximab vedotin was studied in combination with immune checkpoint inhibitors such as nivolumab (NCT02572167) [46] and nivolumab + ipilimumab (NCT01896999) [47] in R/R cHL patients and showed impressive CR rates. A study has been expanded to randomize patients to either receive brentuximab vedotin + nivolumab or brentuximab vedotin + ipilimumab + nivolumab (NCT01896999).

The most notable side effect of brentuximab vedotin is peripheral neuropathy which occurred in about 55% of patients who received brentuximab vedotin monotherapy in the phase 2 study by Younes et al. It resolved or improved in 80% of patients after dose adjustment or stopping therapy. Also, higher rates of neutropenic fever and pulmonary toxicity were observed with chemotherapy regimens incorporating brentuximab vedotin which led to the universal administration of granulocyte colony-stimulating factor (G-CSF) and omitting bleomycin in the brentuximab vedotin + AVD regimen [42].

3.2. Polatuzumab vedotin

Polatuzumab vedotin is a compound of CD79b MAb linked to MMAE [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-medicated killing on the NHL cell which becomes prolonged and more sustained when linked to MMAE [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 of the CD79 subunits into a lysosomal like compartment upon antigen presentation which allows cleavage of the linker between the CD79b MAb and MMAE after internalization of the ADC [33]. Preclinical studies showed that polatuzumab is very active against NHL cells regardless of cell of origin (COO) subtype and degree of CD79b expression. Clinical studies evaluated the combination of polatuzumab with MAbs including rituximab and obinutuzumab in R/R DLBLCL patients with positive results [4, 49]. Polatuzumab was approved in combination with BR in treatment of patients with R/R DLBCL who are ineligible for ASCT and after two lines of therapy. Accelerated FDA approval was based on the initial results of the phase 2 trial (NCT02257567) which randomized 80 patients with R/R DLBCL to BR alone versus polatuzumab plus BR ($n = 40$). Those who received the triple therapy had CR and ORR of 40% and 45% respectively compared to 18% of CR and ORR in the BR group. Median PFS and OS were 7.6 months and 12.4 months respectively in the triple therapy group compared to 2.0 months and 4.7 months respectively in the BR group. These results were regardless of COO and MYC/BCL2 double expression [50].

A recent real world study by Dimou et al. in 61 patients with R/R DLBCL who received polatuzumab plus BR showed that CR and PR were 25% and 18% respectively while median PFS, OS and DOR were 4, 8.5 and 8.5 months respectively. Polatuzumab plus BR may be given as a bridge to CAR T cell therapy. Several ongoing early phase trials in the R/R DLBCL setting are studying the combination of polatuzumab with other therapeutic targets, including venetoclax, lenalidomide and bispecific antibodies [4]. The POLARIX phase III trial (NCT03274492) evaluated the role of polatuzumab at frontline treatment of DLBCL, randomizing patients to receive R-CHOP vs polatuzumab plus RVP and showed improvement in disease free survival and time to next antilymphoma treatment in the polatuzumab group with similar OS at 2 years [51, 52]. Main side effects of polatuzumab plus BR include peripheral neuropathy and cytopenias that were also observed with polatuzumab monotherapy. Those with grade 2 and higher neuropathy are ineligible for polatuzumab. 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 [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 [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% [54]. The most common adverse side effects reported with locastuximab tesirine are hematologic toxicities followed by liver toxicity, nausea and edema [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 [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/

RDLBCL patients respectively in a phase 1 study with most common adverse events being cytopenias and fatigue [56]. A phase 2 study (NCT00867087) involving R/R DLBCL patients evaluated inotuzumab ozagamycin + rituximab followed by high dose chemotherapy and ASCT in high risk patients. ORR was 28.6% and median PFS was 3 months. Of the 18 patients who underwent ASCT, 33% and 22% developed infections and hepatic toxicity respectively [57]. Pinatuzumab vedotin is another CD22 directed ADC with the payload being MMAE, it was evaluated in a randomized phase 2 study (NCT01691898) involving patients with R/R DLBCL and R/R FL resulting in CR in 26% and 5% of the DLBCL and FL groups respectively and an ORR of 60% and 62% in the DLBCL and FL group respectively [58].

Camidanlumab tesirine is CD25 directed ADC with the payload being a PBD dimer. It also showed antitumor activity in neighboring tumor cells that do not express CD25. It was studied In a phase 1 study (NCT02432235) and resulted in an ORR of 71% in 75 patients (CR, $N = 40$) of R/R cHL and R/R NHL expressing CD25 and available for response evaluation. ORR was 93% in the R/R cHL group who relapse withing 6 months of immune checkpoint inhibitors. Most common adverse events were skin rashes and abnormal liver function tests however Guillain-Barre syndrome and peripheral neuropathy were reported in 9% and 6% of patients respectively [59].

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/m [2]/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/m [2]/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 mosentuzumab 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], epcoritamab [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 patienst 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 eludidated in ongoing and future studies.

Funding source

No funding was received for this review.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

The authors have no acknowledgements.

References

[1] D.G. Maloney, T.M. Liles, D.K. Czerwinski, C. Waldichuk, J. Rosenberg, A. Grillo-Lopez, et al., Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma, Blood 84 (8) (1994) 2457–2466.
[2] R. Mohammed, A. Milne, K. Kayani, U. Ojha, How the discovery of rituximab impacted the treatment of B-cell non-Hodgkin's lymphomas, J. Blood Med. 10 (2019) 71–84.
[3] G. Salles, M. Barrett, R. Foà, J. Maurer, S. O'Brien, N. Valente, et al., Rituximab in B-Cell Hematologic Malignancies: a Review of 20 Years of Clinical Experience, Adv. Ther. 34 (10) (2017) 2232–2273.
[4] R. Assi, N. Masri, I. Abou Dalle, J. El-Cheikh, H. Ghanem, AJCHI. Bazarbachi, Polatuzumab Vedotin: current Role and Future Applications in the Treatment of Patients with Diffuse Large B-Cell Lymphoma, Clin. Hematol. Int. 3 (1) (2021) 21–26.
[5] M. Lejeune, M.C. Köse, E. Duray, H. Einsele, Y. Beguin, Caers JJFiI, Bispecific, T-cell-recruiting antibodies in B-cell malignancies, Front. Immunol. 11 (2020) 762.
[6] P. McLaughlin, A.J. Grillo-López, B.K. Link, R. Levy, M.S. Czuczman, M. E. Williams, et al., Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program, J. Clin. Oncol. 16 (8) (1998) 2825–2833.
[7] M.E. Reff, K. Carner, K.S. Chambers, P.C. Chinn, J.E. Leonard, R. Raab, et al., Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20, Blood 83 (2) (1994) 435–445.
[8] P. Colombat, N. Brousse, G. Salles, F. Morschhauser, P. Brice, P. Soubeyran, et al., Rituximab induction immunotherapy for first-line low-tumor-burden follicular lymphoma: survival analyses with 7-year follow-up, Ann. Oncol. 23 (9) (2012) 2380–2385.
[9] I.W. Flinn, R.H. Van der Jagt, B.S. Kahl, P. Wood, T.E. Hawkins, D. MacDonald, et al., An open-label, randomized study of bendamustine and rituximab (br) compared with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in first-line treatment of patients with advanced indolent Non-Hodgkin's Lymphoma (NHL) or Mantle Cell Lymphoma (MCL): the Bright Study, Blood 120 (21) (2012) 902.
[10] M.J. Rummel, N. Niederle, G. Maschmeyer, G.A. Banat, U. von Grünhagen, C. Losem, et al., Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial, Lancet 381 (9873) (2013) 1203–1210.
[11] G. Salles, J.F. Seymour, F. Offner, A. López-Guillermo, D. Belada, L. Xerri, 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 377 (9759) (2011) 42–51.
[12] R. Marcus, A. Davies, K. Ando, W. Klapper, S. Opat, C. Owen, et al., Obinutuzumab for the first-line treatment of follicular lymphoma, N. Engl. J. Med. 377 (14) (2017) 1331–1344.
[13] B. Coiffier, C. Thieblemont, E. Van Den Neste, G. Lepeu, I. Plantier, S. Castaigne, 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 116 (12) (2010) 2040–2045.
[14] T.M. Habermann, E.A. Weller, V.A. Morrison, R.D. Gascoyne, P.A. Cassileth, J. B. Cohn, et al., Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma, J. Clin. Oncol. 24 (19) (2006) 3121–3127.
[15] M. Pfreundschuh, L. Trümper, A. Osterborg, R. Pettengell, M. Trneny, K. Imrie, et al., CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group, Lancet Oncol. 7 (5) (2006) 379–391.
[16] R. Griffiths, J. Mikhael, M. Gleeson, M. Danese, M. Dreyling, Addition of rituximab to chemotherapy alone as first-line therapy improves overall survival in elderly patients with mantle cell lymphoma, Blood 118 (18) (2011) 4808–4816.
[17] H.C. Kluin-Nelemans, E. Hoster, O. Hermine, J. Walewski, M. Trneny, C.H. Geisler, et al., Treatment of older patients with mantle-cell lymphoma, N. Engl. J. Med. 367 (6) (2012) 520–531.
[18] S. Le Gouill, C. Thieblemont, L. Oberic, A. Moreau, K. Bouabdallah, C. Dartigeas, et al., Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma, N. Engl. J. Med. 377 (13) (2017) 1250–1260.
[19] T. Shree, V. Shankar, J.J.K. Lohmeyer, D.K. Czerwinski, J.G. Schroers-Martin, G. M. Rodriguez, et al., CD20-Targeted Therapy Ablates De Novo Antibody Response to Vaccination but Spares Preestablished Immunity, Blood Cancer Discovery 3 (2) (2022) 95–102.
[20] C. Luo, G. Wu, X. Huang, Y. Ma, Y. Zhang, Q. Song, et al., Efficacy and safety of new anti-CD20 monoclonal antibodies versus rituximab for induction therapy of CD20+ B-cell non-Hodgkin lymphomas: a systematic review and meta-analysis, Sci. Rep. 11 (1) (2021) 1–14.
[21] M.J. Rummel, A. Janssens, D. MacDonald, M.M. Keating, J.M. Zaucha, J. Davis, et al., A phase 3, randomized study of ofatumumab combined with bendamustine in rituximab-refractory iNHL (COMPLEMENT A+ B study), Br. J. Haematol. (2021).
[22] J. Hernandez, T. Nielsen, C. Klein, M.J.N. Wenger, Obinutuzumab for the treatment of non-Hodgkin lymphomas, Nat. Biotechnol. 563 (7731) (2018).
[23] L.H. Sehn, N. Chua, J. Mayer, G. Dueck, M. Trněný, K. Bouabdallah, et al., Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial, Lancet Oncol. 17 (8) (2016) 1081–1093.
[24] L.H. Sehn, M. Martelli, M. Trněný, W. Liu, C.R. Bolen, A. Knapp, et al., A randomized, open-label, Phase III study of obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-Cell lymphoma: final analysis of GOYA, J. Hematol. Oncol. 13 (1) (2020) 71.
[25] P. Willard, J. McKay, V. Yazbeck, Role of antibody-based therapy in indolent non-Hodgkin's lymphoma, Leuk. Res. Rep. 16 (2021), 100275.
[26] G. Salles, M. Długosz-Danecka, H. Ghesquières, W. Jurczak, Tafasitamab for the treatment of relapsed or refractory diffuse large B-cell lymphoma, Expert Opin. Biol. Ther. 21 (4) (2021) 455–463.
[27] B.D. Cheson, G. Nowakowski, G. Salles, Diffuse large B-cell lymphoma: new targets and novel therapies, Blood Cancer J. 11 (4) (2021) 68.
[28] W. Jurczak, P.L. Zinzani, G. Gaidano, A. Goy, M. Provencio, Z. Nagy, et al., Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma, Ann. Oncol. 29 (5) (2018) 1266–1272.
[29] W. Jurczak, P.L. Zinzani, G. Hess, G. Gaidano, M. Provencio, Z. Nagy, et al., A Phase IIa, open-label, Multicenter Study of Single-Agent Tafasitamab (MOR208), an Fc-optimized anti-CD19 antibody, in Patients With Relapsed Or Refractory B-cell Non-Hodgkin's lymphoma: Long-Term follow-up, Final Analysis, American Society of Hematology, Washington, DC, 2019.
[30] G. Salles, J. Duell, E.G. Barca, O. Tournilhac, W. Jurczak, A.M. Liberati, et al., Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study, Lancet Oncol. 21 (7) (2020) 978–988.
[31] N.N. Shah, L. Sokol, Targeting CD22 for the Treatment of B-Cell Malignancies, Immunotargets Ther. 10 (2021) 225–236.
[32] S.J. Strauss, F. Morschhauser, J. Rech, R. Repp, P. Solal-Celigny, P.L. Zinzani, et al., Multicenter phase II trial of immunotherapy with the humanized anti-CD22 antibody, epratuzumab, in combination with rituximab, in refractory or recurrent non-Hodgkin's lymphoma, J. Clin. Oncol. 24 (24) (2006) 3880–3886.
[33] A.G. Polson, S.-F. Yu, K. Elkins, B. Zheng, S. Clark, G.S. Ingle, et al., Antibody-drug conjugates targeted to CD79 for the treatment of non-Hodgkin lymphoma, Blood 110 (2) (2007) 616–623.
[34] P. Khongorzul, C.J. Ling, F.U. Khan, A.U. Ihsan, J. Zhang, Antibody-drug conjugates: a comprehensive review, Mol. Cancer Res. 18 (1) (2020) 3–19.
[35] G.K. Berger, A. McBride, S. Lawson, K. Royball, S. Yun, K. Gee, et al., Brentuximab vedotin for treatment of non-Hodgkin lymphomas: a systematic review, Crit. Rev. Oncol. Hematol. 109 (2017) 42–50.
[36] J.M. Connors, W. Jurczak, D.J. Straus, S.M. Ansell, W.S. Kim, A. Gallamini, et al., Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma, N. Engl. J. Med. 378 (4) (2018) 331–344.
[37] A. Younes, A.K. Gopal, S.E. Smith, S.M. Ansell, J.D. Rosenblatt, K.J. Savage, et al., Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma, J. Clin. Oncol. 30 (18) (2012) 2183–2189.
[38] R. Chen, A.K. Gopal, S.E. Smith, S.M. Ansell, J.D. Rosenblatt, K.J. Savage, et al., Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma, Blood 128 (12) (2016) 1562–1566.
[39] J. Kuruvilla, R. Ramchandren, A. Santoro, E. Paszkiewicz-Kozik, R. Gasiorowski, N. A. Johnson, et al., Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study, Lancet Oncol. 22 (4) (2021) 512–524.
[40] C.H. Moskowitz, A. Nademanee, T. Masszi, E. Agura, J. Holowiecki, M.H. Abidi, et al., Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet 385 (9980) (2015) 1853–1862.
[41] C.H. Moskowitz, J. Walewski, A. Nademanee, T. Masszi, E. Agura, J. Holowiecki, et al., Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse, Blood 132 (25) (2018) 2639–2642.
[42] C. Lai, A.M. Kandahari, C. Ujjani, The Evolving Role of Brentuximab Vedotin in Classical Hodgkin Lymphoma, Blood Lymphat. Cancer 9 (2019) 63–71.
[43] A.S. LaCasce, R.G. Bociek, A. Sawas, P. Caimi, E. Agura, J. Matous, et al., Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma, Blood 132 (1) (2018) 40–48.
[44] A. Kumar, C. Casulo, R.H. Advani, E. Budde, P.M. Barr, C.L. Batlevi, et al., Brentuximab vedotin combined with chemotherapy in patients with newly diagnosed early-stage, unfavorable-risk Hodgkin lymphoma, J. Clin. Oncol. 39 (20) (2021) 2257–2265.

[45] J.S. Abramson, J.E. Arnason, A.S. LaCasce, R. Redd, J.A. Barnes, L. Sokol, et al., Brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine for nonbulky limited-stage classical Hodgkin lymphoma, Blood 134 (7) (2019) 606–613.
[46] A.F. Herrera, A.J. Moskowitz, N.L. Bartlett, J.M. Vose, R. Ramchandren, T. A. Feldman, et al., Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma, Blood 131 (11) (2018) 1183–1194.
[47] C.S. Diefenbach, F. Hong, R.F. Ambinder, J.B. Cohen, M.J. Robertson, K.A. David, et al., Ipilimumab, nivolumab, and brentuximab vedotin combination therapies in patients with relapsed or refractory Hodgkin lymphoma: phase 1 results of an open-label, multicentre, phase 1/2 trial, The Lancet Haematology 7 (9) (2020) e660–ee70.
[48] A.J.M. Ferreri, Targeted therapies make room, anti-CD79b agents are coming, Lancet Oncol. 20 (7) (2019) 898–900.
[49] D. Dornan, F. Bennett, Y. Chen, M. Dennis, D. Eaton, K. Elkins, et al., Therapeutic potential of an anti-CD79b antibody–drug conjugate, anti–CD79b-vc-MMAE, for the treatment of non-Hodgkin lymphoma, Blood 114 (13) (2009) 2721–2729.
[50] L.H. Sehn, M. Kamdar, A.F. Herrera, A. McMillan, C. Flowers, W.S. Kim, et al., Randomized phase 2 trial of polatuzumab vedotin (pola) with bendamustine and rituximab (BR) in relapsed/refractory (r/r) FL and DLBCL, J. Clin. Oncol. (2018).
[51] H. Tilly, C. Flowers, J.W. Friedberg, C. Herbaux, F. Morschhauser, L.H. Sehn, et al., POLARIX: a phase 3 study of polatuzumab vedotin (pola) plus R-CHP versus R-CHOP in patients (pts) with untreated DLBCL, Hematol. Oncol. 37 (2019) 68–70.
[52] H. Tilly, F. Morschhauser, L.H. Sehn, J.W. Friedberg, M. Trněný, J.P. Sharman, et al., Polatuzumab vedotin in previously untreated diffuse large B-Cell lymphoma, N. Engl. J. Med. 386 (4) (2021) 351–363.
[53] M. Hamadani, J. Radford, C. Carlo-Stella, P.F. Caimi, E. Reid, O.A. O'Connor, et al., Final results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma, Blood 137 (19) (2021) 2634–2645.
[54] P.F. Caimi, W.Z. Ai, J.P. Alderuccio, K.M. Ardeshna, M. Hamadani, B.T. Hess, et al., Efficacy and safety of loncastuximab tesirine (ADCT-402) in relapsed/refractory diffuse large B-cell lymphoma, Blood 136 (Suppl 1) (2020) 35–37.
[55] V. Ribrag, J. Dupuis, H. Tilly, F. Morschhauser, F. Laine, R. Houot, et al., A dose-escalation study of SAR3419, an anti-CD19 antibody maytansinoid conjugate, administered by intravenous infusion once weekly in patients with relapsed/refractory B-cell non-Hodgkin lymphoma, Clin. Cancer Res. 20 (1) (2014) 213–220.
[56] A. Advani, B. Coiffier, M.S. Czuczman, M. Dreyling, J. Foran, E. Gine, 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. 28 (12) (2010) 2085–2093.
[57] N.D. Wagner-Johnston, A. Goy, M.A. Rodriguez, W.C. Ehmann, P.A. Hamlin, J. Radford, et al., A phase 2 study of inotuzumab ozogamicin and rituximab, followed by autologous stem cell transplant in patients with relapsed/refractory diffuse large B-cell lymphoma, Leuk. Lymphoma 56 (10) (2015) 2863–2869.
[58] F. Morschhauser, I.W. Flinn, R. Advani, L.H. Sehn, C. Diefenbach, K. Kolibaba, 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), The Lancet Haematology 6 (5) (2019) e254–ee65.
[59] M. Hamadani, G.P. Collins, P.F. Caimi, F. Samaniego, A. Spira, A. Davies, et al., Camidanlumab tesirine in patients with relapsed or refractory lymphoma: a phase 1, open-label, multicentre, dose-escalation, dose-expansion study, The Lancet Haematology 8 (6) (2021) e433–ee45.
[60] N.C. Smits, Sentman CLJJoCO, Bispecific T-cell engagers (BiTEs) as treatment of B-cell lymphoma, J. Clin. Oncol. 34 (10) (2016) 1131.
[61] M.-.E. Goebeler, S. Knop, A. Viardot, P. Kufer, M.S. Topp, H. Einsele, et al., Bispecific T-cell engager (BiTE) antibody construct blinatumomab for the treatment of patients with relapsed/refractory non-Hodgkin lymphoma: final results from a phase I study, J. Clin. Oncol. 34 (10) (2016) 1104–1111.
[62] A. Viardot, M.-.E. Goebeler, G. Hess, S. Neumann, M. Pfreundschuh, N. Adrian, et al., Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma, Blood 127 (11) (2016) 1410–1416.
[63] L. Coyle, N.J. Morley, A. Rambaldi, K.D. Mason, G. Verhoef, C. Furness, et al., Open-label, phase 2 study of blinatumomab as second salvage therapy in adults with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma, Blood 132 (2018) 400.
[64] A. Viardot, F. Locatelli, J. Stieglmaier, F. Zaman, Jabbour EJAoh, Concepts in immuno-oncology: tackling B cell malignancies with CD19-directed bispecific T cell engager therapies, Ann. Hematol. 99 (10) (2020) 1–15.
[65] S.J. Schuster, N.L. Bartlett, S. Assouline, S.-.S. Yoon, F. Bosch, L.H. Sehn, et al., Mosunetuzumab induces complete remissions in poor prognosis non-Hodgkin lymphoma patients, including those who are resistant to or relapsing after chimeric antigen receptor T-cell (CAR-T) therapies, and is active in treatment through multiple lines, Blood (2019).
[66] L. Wang, Li l-r, Young KHJJoH, Oncology. New agents and regimens for diffuse large B cell lymphoma, J. Hematol. Oncol. 13 (1) (2020) 1–23.
[67] K. Patel, J.-.M. Michot, A. Chanan-Khan, H. Ghesquieres, K. Bouabdallah, J. C. Byrd, et al., Safety and anti-tumor activity of plamotamab (XmAb13676), an anti-CD20 x anti-CD3 bispecific antibody, in subjects with relapsed/refractory non-Hodgkin's lymphoma, Blood 138 (2021) 2494.
[68] M.R. Clausen, P. Lugtenburg, M. Hutchings, P.W. Johnson, K.M. Linton, D.J. Lewis, et al., Subcutaneous epcoritamab in patients with relapsed/refractory B-cell non-Hodgkin lymphoma: safety profile and antitumor activity, J. Clin. Oncol. (2021).
[69] R. Bannerji, J.N. Allan, J.E. Arnason, J.R. Brown, R. Advani, S.M. Ansell, et al., Odronextamab (REGN1979), a human CD20 x CD3 bispecific antibody, induces durable, complete responses in patients with highly refractory B-cell non-Hodgkin lymphoma, including patients refractory to CAR T therapy, Blood 136 (2020) 42–43.