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Novel biologic therapies in relapsed or refractory diffuse large B cell lymphoma: CAR-T is not the only answer.

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ABSTRACT

Patients with diffuse large B-cell lymphoma who have refractory or relapsed disease following first line treatment have a poor prognosis when treated with conventional therapies. Significant efforts have been made in recent years to bring a broad spectrum of novel targeted therapies, the most noteworthy of which is chimeric antigen receptor T-cell therapy (CAR-T). Not all patients are eligible for CAR-T given the relatively high risk of complications and limited availability. Here we discuss promising novel biologic therapies that have been introduced in the last few years and go over ongoing clinical trials in the field.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) remains the most common subtype of non-Hodgkin lymphoma [1, 2]. The introduction of the anti-CD20 antibody rituximab, which was the first biologic agent to be used in the treatment of lymphoid malignancies, was an important turning point in the management of this malignancy. Following its approval by the FDA in 2006 the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) became the frontline treatment for DLBCL, offering a complete response rate above 60% [3].

Unfortunately, patients who develop disease relapse or have disease refractory to R-CHOP, have a poor prognosis [4]. The standard of care of patients with relapsed or refractory DLBCL (R/R DLBCL) has been high dose chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT). Not all patients are eligible for ASCT, and this treatment modality does not guarantee long term survival. A multitude of clinical trials have led to FDA approvals for novel therapies for R/R DLBCL including small molecule inhibitors (BTK inhibitors, exportin inhibitors), new monoclonal antibodies (mAb) with various mechanisms of action, and most finally chimeric antigen receptor T-cell therapies (CAR-T). Multiple novel mAbs have been introduced during recent years including new antibody-drug conjugates (ADC), mAbs with enhanced antibody dependent cellular cytotoxicity (ADCC) and Bispecific T-cell engagers (BiTes). These therapies offer an opportunity for therapy for patient not eligible for intensive therapy and those who have disease refractory to such treatments, without compromising on the chance of a favorable outcome.

Here we review novel non cellular biologic agents that have been introduced in the last 5 years in the treatment of R/R DLBCL, highlighting their mechanisms of action, landmark clinical trials, and main side effects.

2. Antibody-drug conjugates

2.1. Polatuzumab-vedotin

Polatuzumab-Vedotin (DCDS4501A) is an ADC that combines an antibody targeted to against CD-79b, a component of the B-cell receptor (BCR) signaling pathway, to vedotin, a microtubule disrupting agent [5]. In an initial phase 1 trial, Polatuzumab showed activity as a single agent with overall response rates (ORR) of up to 56% in a cohort of patients with non—Hodgkin's lymphoma (NHL) [6]. It was granted FDA approval as combination therapy with bendamustine and rituximab (BR) in 2019 after publication of the GO29365 trial results, in which 80 patients with R/R DLBCL, who were transplant ineligible, were randomized in a 1:1 fashion to receive either BR or polatuzumab-BR. The complete response (CR) rate was significantly higher in the pola-BR group as compared to BR (40.0% v 17.5%; $P = .02$) with 15% showing responses lasting more than 20 months [7]. Similar results were seen in the phase 2 ROMULUS trial, evaluating polatuzumab to the anti CD22 ADC pinatuzumab when both are combined to rituximab. This trial showed an overall response rate (ORR) of 54% with polatuzumab-rituximab with responses lasting for a median of 13.4

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months. [8] The main adverse events recorded in trials included fatigue, gastrointestinal disturbances (diarrhea, nausea, constipation, loss of appetite) as well as hematologic toxicities (anemia, neutropenia, and thrombocytopenia) with the latter occurring more commonly when bendamustine is added to the treatment. The combination of polatuzumab and BR is listed as a preferred regimen by the NCCN for second or subsequent line therapy for R/R DLBCL [9].

2.2. Loncastuximab-tesirine

Loncastuximab tesirine (ADCT-402) is a mAb targeted against CD-19 that is conjugated to tesirine, a pyrrolobenzodiazepine, which exerts its anti-tumor activity by forming interstrand crosslinks in DNA at the minor groove [10, 11]. The use of the medication as a single agent was evaluated in a phase 2 multicenter trial (LOTIS-2) that enrolled 145 patients with R/R DLBCL. The majority of patients were heavily pretreated and had received more than 3 prior lines of therapy, only a minority had undergone ASCT or CAR-T cell therapy. The reported ORR was 48% with about half of those who had a response achieving a CR. Interestingly, around half of patients who achieved a CR had no evidence of relapse at the study data cutoff [12]. Additionally, to answer the question of whether subsequent CD-19 directed CAR-T cell therapy would still be effective after loncastuximab, 14 patients from the aforementioned trial and from a previous phase 1 trial [13] were evaluated after receiving an anti-CD-19 CAR-T. Half of these patients showed a response to CAR-T and CD-19 expression was not affected in most patients in the study [14]. Locastuximab-tesirine is well tolerated, it is mainly responsible for cytopenias with a low incidence of grade 3 or more neutropenia (26%). Non-hematologic side effects are infusion reactions fatigue, nausea and cough, most of which are grade 1–2. [12] Premedication with dexamethasone 4 mg orally, twice daily for 3 days starting on the day prior to treatment is recommended to prevent infusion reaction. Additionally, avoidance of prolonged exposure to sunlight is advised to decrease the risk of skin rashes.

2.3. Brentuximab-vedotin

In contrast to the two aforementioned ADCs, brentuximab vedotin (Bv) has gained momentum in both B and T-cell lymphoid malignancies. This is a CD-30 targeted mAb that is, similarly to polatuzumab, conjugated to vedotin. CD-30 is specific to immune tissues and is expressed on both B and T lymphocytes making it a reasonable target for multiple lymphoid malignancies, among which Hodgkin's Lymphoma, anaplastic large cell lymphoma, cutaneous T-cell lymphoma and DLBCL [15].

The efficacy of Bv in R/R DLBCL was proven in a phase 2 trial that included 49 patients with CD30 positive R/R DLBCL, where it was given at a dose of 1.8 mg/kg in 21-day cycles and was continued until disease progression or unacceptable toxicity. Treatment resulted in a response in 44% of patients with 17% achieving CR. Interestingly, there was no correlation between the strength of CD30 expression and response [16]. Similar to previously mentioned ADCs, Bv is known to cause hematologic toxicities with neutropenia being the most significant. In addition, peripheral neuropathy is a more specific side effect for Bv that can be significant and may become irreversible. Neuropathy is usually sensory and may result in dose reduction or discontinuation of the drug depending on the severity of symptoms [17] (Table 1).

3. ADCC inducing monoclonal antibodies

3.1. Tafasitamab

Tafasitamab (MOR208) is a novel anti-CD-19 mAb that takes advantage of novel antibody engineering technology to improve the ADCC potential of the antibody's Fc domain. Pre-clinical studies showed enhanced NK-cell activity when tafasitamab is incubated with malignant cells from patients with CLL [18].

The clinical efficacy of tafasitamab was evaluated in the single-arm, multicenter phase 2 trial L-MIND, in which tafasitamab was given in combination with lenalidomide for up to 12 cycles, followed by tafasitamab maintenance, to patients with R/R DLBCL who were not eligible for ASCT. Long lasting responses were seen with an ORR of 60% and an impressive CR of 43% [19, 20]. The L-MIND trial lead to an emergency use FDA approval for tafasitamab with lenalidomide in July 2020 [21]. The most common and serious side effect of the combination is neutropenia, which usually recovers within 1 week with the use of myeloid growth factor. Other hematologic toxicities including anemia and thrombocytopenia are also common. Non-hematologic side effects include diarrhea, skin rash and fatigue, and are rarely grade 3 or more [19].

Moreover, the phase Ib FIRST-MIND trial has proven tolerability of the combination of tafasitamab/lenalidomide with R-CHOP in the first line setting [22]. Further trials to evaluate the efficacy of this regimen are ongoing. (NCT04824092)

3.2. Bispecific antibodies

Antibodies targeting both a target epitope on the tumor cell and a target epitope on an immune cell are called bispecific antibodies (bsAbs). They allow to facilitate immune-cell engagement and activation of ADCC against tumor cells in an HLA-independent way. More than 100 bsAb formats currently exist with various biochemical structure and conformation. In the majority of cases, the target immune cells are T-cells, and the bsAbs are directed against CD3. Sometimes, the target immune cells are NK-cells and macrophages, and the bsAbs are directed

Table 1
List of novel biologic therapies in relapsed or refractory diffuse large B-cell lymphoma. (Bispecific antibodies excluded) CR: complete response rate, ORR: overall response rate.

Antibody	Target	Combination	Regimen	Landmark trial	Efficacy	Special considerations
Polatuzumab-Vedotin	CD79b	Bendamustine / Rituximab	1.8 mg/kg IV on day 2 of cycle 1 then on day 1 of subsequent cycles. BR according to standard regimen in 21 day cycles	Sehn et al. 2020 (GO29365)	CR 40.0% with pola-BR	
polatuzumab-vedotin	CD79b	–	1.8 mg/kg IV	Morschhauser et al., 2019. (ROMULUS)	ORR of 54%	
Loncastuximab-tesirine	CD19	–	150 mcg/kg IV on cycles 1 and 2 then 75 mcg/kg every 21 days for a maximum of 1 year	Caimi et al., 2021 (LOTIS-2)	ORR of 48%	Sunlight avoidance is advised. Dose needs to be adjusted if BMI>35 kg/m2
Brentuximab-vedotin	CD30	–	1.8 mg/kg IV every 21	Jacobsen et al., 2015	ORR of 44%, CR of 17%	Monitor for neuropathy that can become irreversible
Tafasitamab	CD19	Lenalidomide	Tafasitamab 12 mg/kg weekly for the first 3 months then every other week. Lenalidomide 25 mg orally on days 1–21 in 28-day cycles.	Salles et al., 2020 (L-MIND)	ORR of 60%, CR of 43%	Myeloid growth factor support needed with treatment.

against CD16A. Regarding the tumor cells, the targeted antigen is often CD19 or CD20 in B-cell malignancies. The chemical structures of the bsAbs are numerous. They can be classified into two distinct groups: bsAbs without Fc region and bsAbs with an IgG-like structure (Fig. 1). The former are made of two single-chain antibodies with a linker. They have a small size and a short half-life, needing frequent or continuous administration, which is a serious limitation. The latter are made of Fab and Fc regions, in various associations according to the subclass of bsAbs. These bsAbs are bigger and their half-lifes are longer, allowing for less frequently administered molecules. The majority of bsAbs with an IgG-like structure have a Fc domain with a reduced binding activity to FcγR in order to decrease cytokine release syndrome (CRS) frequency, improve tolerance, reduce treatment interruptions, and maximize efficacy (Table 2).

3.3. Blinatumomab

Blinatumomab (MT103) is the first bsAb approved in hematological malignancies. This bsAb is approved for R/R B-cell acute lymphoblastic leukemia (ALL) and in B-cell ALL with MRD positivity. It is made of a single chain targeting CD19 and a single chain targeting CD3 (BIspecific T-cell Engager (BiTE) format) (Fig. 1). It does not contain a Fc domain and has a short half-life necessitating a continuous infusion. Blinatumomab was also tested in B-NHL, especially DLBCL in several trials. In a phase 1 study including various B-NHL subtypes [23], the found target dose for blinatumomab was 60 μg/m^2/day. Below this dose, the response rates were poor, and above this dose, neurologic events were dose-limiting toxicities (DLT). Among the 35 patients treated at the target dose, the ORR was 69% (55% for the 11 DLBCL patients). The median DOR was 404 days. Grade 3 neurologic adverse events occurred in 22% of patients, which is high, even with strategies attempting to mitigate neurologic toxicity. In a phase 2 study with the majority of patients receiving blinatumomab in a step-up dosing (9–28–112 μg/day with weekly dose increases) [24], among 21 evaluable patients with R/R DLBCL (median of 3 prior lines of therapy), the ORR was 43% and the CR rate 19% after 1 cycle. Here again, neurotoxicity was a limitation, with 4/5 patients who stopped blinatumomab due to adverse events having neurologic events. In another phase 2 study, patients received blinatumomab as a second salvage regimen after a first salvage with platinum-based chemotherapy [25]. Blinatumomab was administered with a step-up dosing (9–28–112 μg/day) in a 70-day cycle and then in an optional 28-day cycle. The ORR of 41 patients after 12 weeks of treatment was 37% and the CR rate 22%. There were only 1 grade 3 CRS but 24% grade 3 neurologic events. Only 46% of patients completed the first cycle of treatment, mainly due to disease progression.

3.4. Glofitamab

Glofitamab (RG6026) is a humanized mouse IgG1-based CD20/CD3 bsAb with a modified Fc devoid of FcγR and complement binding, and with 2 binding sites to CD20 (derived from the type II CD20 IgG1 glycoengineered Obinutuzumab) in order to increase affinity for CD20$^+$ target cells (Fig. 1). In a recently presented phase 1 study, patients with

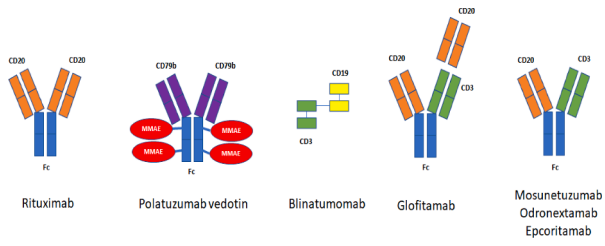

Fig. 1. Simplified structure of current immunotherapies in DLBCL. MMAE = monomethyl auristatin E.

B-NHL received Glofitamab in two different step-up dosing regimens (2.5–10–16 mg or 2.5–10–30 mg) in order to mitigate the risk of CRS [26]. Glofitamab was administered IV every three weeks for up to 12 cycles. Moreover, in order to reduce the prevalence and severity of CRS, Obinutuzumab was given 7 days before the first Glofitamab administration, to induce a first B-cell depletion. Thirty-eight patients were included: 28 patients had an aggressive NHL (12 patients with DLBCL) and ten patients an indolent NHL. The median number of prior lines of therapy was 3 (range 1–12): 71% of patients were refractory to the last treatment line. For the 24 evaluable patients with an aggressive NHL, the ORR and the CR rate were 50% and 29%, respectively. Fifty-eight percent of patients experienced any grade CRS, only 1 patient experienced grade $\geq$ 3 CRS, none experienced grade $\geq$ 3 neurologic events.

Preclinical data have shown that treatment with Glofitamab can lead to upregulation of programmed cell death protein 1 (PD-1) and programmed cell death-ligand-1 (PD-L1) on T-cells and tumor cells, respectively, as a mechanism of tumor escape to the immune system. As a result, a phase 1 dose escalation study combining Glofitamab with Atezolizumab, a monoclonal antibody directed against PD-L1, was developed and the preliminary data of this trial have already been presented [27]. Obinutuzumab pre-treatment was also administered before Glofitamab. Atezolizumab was added from cycle 2 and given on the same day as Glofitamab. For the 36 evaluable patients (31 with aggressive NHL, 5 with indolent NHL), the ORR was 36% and the CR rate was 17%, with higher response rates for the highest doses of Glofitamab.

3.5. Mosunetuzumab

Mosunetuzumab (RG7828, RO7030816) is a humanized mouse heterodimeric IgG1-based CD20/CD3 bsAb with a modified Fc devoid of FcγR and complement binding, with only 1 binding site to CD20 (Fig. 1). Mosunetuzumab is being tested in monotherapy or in combination with CHOP-like regimens or other immunotherapies, both in the R/R and in the frontline settings. At ASH 2019, first results of the Group B of the phase 1/1b GO29781 study, a dose escalation and dose expansion trial in which Mosunetuzumab is administered in R/R B-NHL patients with a step-up dosing on days 1, 8 and 15 of cycle 1, then as a fixed dose on day 1 of subsequent 21-day cycles (up to 17 cycles), were presented in the plenary session [28]. Among the 270 patients who received Mosunetuzumab, 67% had an aggressive NHL and 32% had an indolent NHL. The ORR and CR rate were 37% and 20% in aggressive NHL, respectively. In this study, 30 patients had received prior CAR T-cells; for this specific subpopulation, the ORR and CR rate were 39% and 22%. This means that bsAbs may be effective even in patients relapsing after CAR T-cells. For patients with aggressive NHL, 70% had ongoing responses at 16 months. The tolerance was excellent, with 29% of patients had all grades CRS, but only 1% grade $\geq$ 3 CRS and grade $\geq$ 3 neurologic adverse events.

Another cohort of the GO29781 study consisted in administering Mosunetuzumab subcutaneously (every 3 weeks up to 12 cycles) in order to reduce CRS severity and frequency, to reduce healthcare resource utilization, and to improve convenience for patients. First results were presented at ASH 2020 [29]. Among the 22 patients who were evaluable for efficacy analyses, the ORR and CR rate were 60% and 20% in aggressive NHL, respectively. After a median of 6.9 months on study, all but 1 CR patient remained in remission. SC Mosunetuzumab was well tolerated with no grade $\geq$ 2 CRS at doses $<$ 13.5 mg. All CRS occurred during cycle 1 and resolved without intensive care unit admission, tocilizumab administration or vasopressors. Interestingly, lower peak IL-6 levels were observed.

In the ongoing GO40515 phase 1b/2 study, IV Mosunetuzumab was administered in combination to CHOP (M-CHOP) for 6 21-day cycles in previously untreated DLBCL and in some R/R NHL [30]. Mosunetuzumab was administered with a step-up dosing during cycle 1 in order to mitigate CRS severity. For patients in PR or in SD after 6 cycles, Mosutenuzumab could be administered in monotherapy for up to 11

Table 2
Main results of the phase 1/2 trials with bispecific antibodies in relapsed or refractory diffuse large B-cell lymphoma. IV = intravenous; SC = subcutaneous.

Drugs	Blinatumomab	Glofitamab	Mosunetuzumab	Mosunetuzumab	Odronextamab	Epcoritamab
Targets	CD19/CD3	CD20/CD3	CD20/CD3	CD20/CD3	CD20/CD3	CD20/CD3
Structure	single chain	IgG-like	IgG-like	IgG-like	IgG-like	IgG-like
Administration	IV	IV	IV	SC	IV	SC
Study phase	2	1	1	1	1	1
Number of patients	41	38 (24 with evaluable aggressive NHL)	270 (116 with aggressive NHL)	23 (15 with evaluable aggressive NHL)	136 (78 with DLBCL)	68 (46 with DLBCL)
ORR (for aggressive NHL)	**37%**	**50%**	**37%**	**60%**	DLBCL $\geq$ 80 mg without previous CART (n = 11) **55%** DLBCL $\geq$ 80 mg with previous CART (n = 24) **33%**	dose 12–60 mg (n = 22): **68%** dose 48–60 mg (n = 11): **91%**
CR (for aggressive NHL)	**22%**	**29%**	**20%**	**20%**	DLBCL $\geq$ 80 mg without previous CART (n = 11) **55%** DLBCL > 80 mg with previous CART (n = 24) **21%**	dose 12–60 mg (n = 22): **46%** dose 48–60 mg (n = 11): **55%**
Grade $\geq$ 3 CRS	**2%**	**3%**	**1%**	**0%**	**7%**	**0%**
Grade $\geq$ 3 neurotoxicity	**24%**	**0%**	**1%**	**0%**	**3,70%**	**3%**
References	*Coyle, Leuk Lymph 2020*	*Hutchings, ASH 2020*	*Matasar, ASH 2020*	*Phillips, ASH 2020*	*Bannerji, ASH 2020*	*Hutchings, ASH 2020*

additional cycles. Forty-three patients were included (median age 66 years old (range 39–87)): 36 patients with untreated DLBCL and 7 patients with R/R NHL. In the 27 evaluable untreated DLBCL patients, the ORR was 96% and the CR rate 85There was no grade $\geq$ 3 CRS and no immune effector cell-associated neurotoxicity syndrome (ICANS) of any grade.

In an ongoing phase 1 /2 study, Mosunetuzumab monotherapy was evaluated in first line in DLBCL for elderly patients unable to receive a chemoimmunotherapy like R-CHOP [31]. Mosunetuzumab was administered in a step-up dosing for cycle 1, then as a fixed dose for up to 17 cycles. Nineteen patients were included, the median age was 84 years old (range 67–100). Forty-seven percent of patients experienced a CRS; all CRS were grade 1. No grade $\geq$ 3 neurologic event occurred. The ORR was 58% and the CR rate 42%.

3.6. Odronextamab

Odronextamab (REGN1979) is a fully human IgG4-based heterodimeric CD20/CD3 bsAb (monovalent CD20 and monovalent CD3 binding sites). It is hinge-stabilized and its Fc domain has an altered function. In an ongoing phase 1 study including patients with R/R indolent or aggressive NHL (NCT02290951), Odronextamab was administered weekly up to week 12 (dose range 0.03–320 mg), then every two weeks as a maintenance phase [32]. To mitigate the risk of CRS, there was an initial step-up dosing and a premedication with dexamethasone. Currently, 136 patients were included, 78 patients with R/R DLBCL, mostly heavily pretreated. No DLT was reported and the MTD was not reached. Regarding toxicities, 61% of patients experienced a CRS (but only 7% grade $\geq$ 3), and 3.7% experienced a grade $\geq$ 3 ICANS. Among the 11 DLBCL patients who had received a dose of Odronextamab $\geq$ 80 mg without previous CAR T-cells, 6/11 (55%) achieved both a response and a CR. Among the 24 DLBCL patients who had received a dose $\geq$ 80 mg with previous CAR T-cells, 8/24 (33%) achieved a response and 5/24 (21%) a CR.

3.7. Epcoritamab

Epcoritamab (GEN3013) is a humanized mouse IgG1-based heterodimeric CD20/CD3 bsAb, with a modified Fc region. It is administered subcutaneously. In an ongoing phase 1 /2 study (NCT03625037) in patients with R/R DLBCL, FL or MCL, Epcoritamab was administered in 28-day cycles until disease progression or unacceptable toxicity (q1w cycles 1–2, q2w cycles 3–6, then q4w) with an initial step-up dosing and a premedication with steroids in order to reduce CRS occurrence[33]. Among 68 included patients, 46 had R/R DLBCL (dose range 0.0128–60 mg). The RP2D was 48 mg. Fifty nine percent of patients experiences all grades CRS, with no grade $\geq$ 3 CRS. Two patients experienced a grade 1 ICANS, 2 patients a grade 3 ICANS. In DLBCL patients, the ORR and CR rate were 68% and 46% for those who had received a dose between 12 and 60 mg, and 91% and 55% for those who had received a dose between 48 and 60 mg, respectively. Impressive results were also observed in FL, MCL, and in patients relapsing after CAR T-cells.

3.8. Clinical trials

The field of immunotherapies in DLBCL is expanding exponentially and increases the different therapeutic options that clinicians may offer to their patients. The development of new molecules, in particular ADC and bsAbs, have greatly improved the therapeutic armamentarium. New molecules are in preclinical development, and there is a possibility of new targets on tumor cells, but also of toxins for ADC, and recruited immune cells for bsAbs (bsAbs targeting CD16A and recruiting NK cells and macrophages).

Many clinical trials of mAbs, ADC or bsAbs are recruiting or will recruit patients with DLBCL (**Table 3**). These Abs are being tested in association with conventional chemotherapies. For example, Glofitamab is associated with gemcitabine and oxaliplatin and compared to Rituximab + gemcitabine + oxaliplatin in R/R DLBCL in a phase 3 trial. These antibodies are also being tested in combination with other targeted therapies, especially other immunotherapies. For instance, Mosunetuzumab is combined to Polatuzumab vedotin in a phase 1 / 2 trial.

There are several challenges in the development of these new drugs. First, it will be interesting to test these antibodies earlier in the treatment of DLBCL, as in first line. Thus, in a phase 2 trial, Glofitamab will be combined to R-CHOP in the frontline setting for patients with DLBCL. Another challenge is to define the place of these treatments in relation to other innovative therapies, like CAR T-cells. Currently, there is no direct comparison between CAR T-cells and bsAbs. In our opinion, bsAbs could be alternative options for patients not eligible to CAR T-cells or for those relapsing after CAR T-cells. A phase 2 study is recruiting patients with B-NHL and a relapse after CAR T-cells.

4. Conclusion

In this review, we described new mAbs, ADC and bsAbs developed in the field of DLBCL. An increasing number of clinical trials is testing them, alone or in combination with conventional chemotherapies, targeted therapies, or other immunotherapies like immune checkpoint

Table 3
Recruiting or not yet recruiting clinical trials with mAbs, ADC or bsAbs in DLBCL. Source: ClinicalTrials.gov. *R* = Rituximab; GemOx = gemcitabine + Oxaliplatin; ASCT = autologous stem cell transplantation.

Type of immunotherapy	Drugs	Target antigens	Disease	Study phase	NCT number
mAb	Rituximab + Acalabrutinib + Lenalidomide + Tafasitamab +/- CHOP	CD19	Untreated non-GC DLBCL	2	NCT04978584
mAb	Tafasitamab + Lenalidomide + R-CHOP vs R-CHOP	CD19	Untreated DLBCL	3	NCT04824092
mAb	*Tafasitamab + Lenalidomide + R*	CD19	Untreated DLBCL	2	NCT04974216
mAb	Tafasitamab alone or + Lenalidomide or + parsaclisib in R/R DLBCL Tafasitamab + Lenalidomide + R-CHOP in untreated DLBCL	CD19	Untreated and R/R DLBCL	1	NCT04661007
ADC	Loncastuximab tesirine + Ibrutinib	CD19	R/R DLBCL R/R MCL	1/2	NCT03684694
ADC	Loncastuximab tesirine + R-CHOP	CD19	Untreated DLBCL	1	NCT04974996
ADC	Loncastuximab tesirine + R vs R-GemOx	CD19	R/R DLBCL	3	NCT04384484
ADC	R-GemOx +/- Polatuzumab vedotin	CD79b	R/R DLBCL	3	NCT04182204
ADC	R-ICE + Polatuzumab vedotin	CD79b	R/R DLBCL	2	NCT04665765
ADC	R-ICE +/- Polatuzumab vedotin	CD79b	R/R DLBCL	3	NCT04833114
ADC	R-miniCHOP vs R-miniCHP + Polatuzumab vedotin	CD79b	Untreated DLBCL	3	NCT04332822
ADC	Polatuzumab vedotin + venetoclax + R-CHP	CD79b	Untreated DLBCL (Bcl-2 positive in immunohistochemistry)	1	NCT04790903
ADC	Polatuzumab vedotin + R-CHP	CD79b	Untreated High-grade B-cell lymphoma	2	NCT04479267
ADC	Polatuzumab vedotin + R-CHP + etoposide	CD79b	untreated aggressive B-NHL	1	NCT04231877
ADC	Polatuzumab vedotin + ViPOR (Venetoclax Ibrutinib Prednisone Obinutuzumab Lenalidomide)	CD79b	B-NHL	1	NCT04739813
ADC	Rituximab + Lenalidomide +/- Brentuximab vedotin	CD30	R/R DLBCL	3	NCT04404283
ADC	Brentuximab vedotin + R-DHAP	CD30	R/R DLBCL	1/2	NCT03356054
ADC	STRO-001	CD74	B-cell lymphoma myeloma	1	NCT03424603
bsAb	Blinatumomab + Lenalidomide	CD19/CD3	B-NHL	1	NCT02568553
bsAb	Glofitamab	CD20/CD3	R/R LBCL	1	NCT04657302
bsAb	Glofitamab-GemOx vs R-GemOx	CD20/CD3	R/R DLBCL	3	NCT04408638
bsAb/ADC	Mosutenuzumab as consolidation after immunochemotherapy (cohort A) Mosunetuzumab alone in elderly/unfit patients (cohort B) Mosunetuzumab + Polatuzumab vedotin in elderly/unfit patients (cohort C)	CD20/CD3 CD79b	Untreated DLBCL	1/2	NCT03677154
bsAb	Glofitamab + R-CHOP	CD20/CD3	Untreated DLBCL	1	NCT03467373
bsAb	Glofitamab + R-CHOP	CD20/CD3	Untreated DLBCL	2	NCT04980222
bsAb/ADC	R-CHOP + Glofitamab R-CHP + Polatuzumab vedotin + Glofitamab	CD20/CD3 CD79b	Untreated DLBCL	1/2	NCT04914741
bsAb	Glofitamab	CD20/CD3	B-NHL relapsing after CAR T-cells	2	NCT04703686
bsAb	Glofitamab or Mosunetuzumab after anti-CD19 CAR T-cells	CD20/CD3	R/R DLBCL	2	NCT04889716
bsAb	Odronextamab	CD20/CD3	R/R B-NHL	1	NCT02290951
bsAb	Epcoritamab	CD20/CD3	R/R B-NHL	1/2	NCT04542824
bsAb	Epcoritamab	CD20/CD3	R/R B-NHL	1/2	NCT03625037
bsAb	Epcoritamab vs R-GemOx or R-Bendamustine	CD20/CD3	R/R DLBCL	3	NCT04628494
bsAb	Epcoritamab + various combinations: Arm 1: + R-CHOP untreated DLBCL Arm 2: + *R* + Lenalidomide R/R FL Arm 3: + R-Bendamustine untreated FL Arm 4: + R-DHAC/X R/R DLBCL eligible for ASCT Arm 5: + GemOx R/R DLBCL ineligible for ASCT	CD20/CD3	untreated and R/R DLBCL untreated and R/R FL	1/2	NCT04663347
bsAb	XmAb13676	CD20/CD3	R/R B-NHL	1	NCT02924402

inhibitors. These studies are including patients both in the R/R and frontline settings, and these therapies will have a more important role and will be used earlier in the near future. Results coming from phase 1 and 2 studies are very promising, with strategies used in order to avoid major toxicities like CRS and ICANS resulting from the use of bsAbs. Phase 3 trials are starting their recruitment. The main challenge will be defining the place of these immunotherapeutic approaches in relation to other treatments like.

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There is no conflict of interest to declare for this project.

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