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REVIEW ARTICLE

Advances in Immunotherapy for Diffuse Large B Cell Lymphoma

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Abstract
Diffuse large B cell lymphoma (DLBCL) is a heterogeneous disease that is normally treated with combination chemotherapy combined with the anti-CD20 monoclonal antibody rituximab. Although about two-thirds of patients are cured with initial chemo-immunotherapy, a sizable minority of patients will have relapsed or refractory (r/r) DLBCL. Standard therapy for r/r DLBCL is salvage chemotherapy followed by autologous stem cell transplantation (ASCT); however, a minority of patients have long-term remission with this approach. In recent years, there has been a proliferation of immunotherapies for the treatment of DLBCL that have expanded our treatment options for these patients, providing the opportunity for durable remissions that were not previously possible. In this review, we discuss these novel immunotherapies, including monoclonal antibodies, antibody–drug conjugates, bispecific antibodies and chimeric antigen receptor (CAR) T cells. The plethora of novel agents leaves patients with more therapeutic options, but leaves the practitioner faced with challenging decisions regarding the timing and indications for use of these immunotherapies. Although studies are ongoing, no agents have been verified as alternatives to standard salvage therapy followed by ASCT at first relapse. The opportunity for durable response and broad age range eligibility makes a strong case for CAR T cells to be used as third-line therapy. The remainder of the agents discussed can be useful in specific clinical scenarios including in patients who are not candidates for ASCT or CAR T cells, as bridging therapy to CAR T cells, or in the r/r setting after CAR T cell therapy failure.

Key Points

Novel immunotherapies are revolutionizing the landscape of diffuse large B cell lymphoma treatment.

Chimeric antigen receptor T cells appear to provide an opportunity at durable remission and should be considered standard third-line treatment for eligible patients.

1 Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common form of non-Hodgkin's lymphoma (NHL), with more than 18,000 new cases per year being diagnosed in the United States [1]. Recent work has demonstrated that DLBCL is a heterogeneous disease that can be subdivided into various subgroups based on underlying molecular disruptions [2–5]. These subtypes have varying prognosis and rates of relapse, but despite our understanding of the molecular drivers of DLBCL, the first-line therapy remains a standard combination of chemo-immunotherapy. Frontline therapy of DLBCL consists of rituximab, a monoclonal antibody directed against CD20, combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). The primary advance in first-line therapy of DLBCL in the last 20 years was the addition of rituximab to the prior standard CHOP regimen (R-CHOP), which was associated with an improvement in overall survival (OS) [6, 7]. About a third of patients will have relapsed and/or refractory (r/r) disease. Standard second-line therapy involves conventional salvage combination chemotherapy followed by autologous stem cell transplantation (ASCT) in patients with chemosensitive disease [8, 9]. For those patients who fail to respond to salvage chemotherapy or who relapse after ASCT, CD19-directed chimeric antigen receptor (CAR) T cell therapy with axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), or lisocabtagene maraleucel (liso-cel) are standard of care

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(SOC) options [10-12]. Although ASCT and CAR T cell therapy offer patients an opportunity for durable remission, many patients are not eligible for ASCT and/or CAR T cell therapy or relapse after these treatments. Various immunotherapies, including novel CAR T cell therapies, monoclonal antibodies, antibody–drug conjugates (ADCs), and bispecific antibodies, have shown efficacy in patients with multiply r/r DLBCL. This proliferation of new immunotherapy options presents a dilemma regarding selection and sequence of novel therapies. This review will focus on outlining these therapies, including those that have attained Food and Drug Administration (FDA) approval (summarized in Table 1) as well as those under study (summarized in Table 2), and will provide a clinical framework for tailored decision making given the plethora of novel options.

2 Monoclonal Antibodies

2.1 Obinutuzumab

Despite the success of the CD20 monoclonal antibody rituximab in DLBCL, some patients develop rituximab resistance through various mechanisms [13–15]. Obinutuzumab is a humanized glycoengineered type II anti-CD20 monoclonal antibody that has demonstrated greater antibody-dependent cytotoxicity, direct cell death, and induction of phagocytosis than rituximab [16]. Obinutuzumab prolonged progression-free survival (PFS), but not OS compared to rituximab in low-grade lymphomas, and as a result, was approved by the FDA in the front-line setting for follicular lymphoma. In a large, randomized, phase 3 trial in DLBCL, however, there was no improvement in the outcome of patients with newly diagnosed DLBCL treated with obinutuzumab combined with CHOP compared to patients treated with R-CHOP [17, 18]. There may be a role for obinutuzumab in the r/r setting, however, as a phase 2 study evaluating obinutuzumab as a single agent found an overall response rate (ORR) of 37%, with 20% of rituximab-resistant patients having a response [19].

2.2 Tafasitamab

Tafasitamab is an Fc-engineered, humanized CD19 antibody. It was initially tested for safety and efficacy in r/r NHL as a single agent in a phase 2a study and produced a response rate of 26% among patients with DLBCL ($n = 35$), with responses lasting longer than 2 years in some patients. Common adverse events included infusion reactions in 12% of patients and neutropenia [20]. Patients with r/r DLBCL who were ineligible for ASCT were enrolled into the L-MIND study, a phase 2 study evaluating the efficacy of tafasitamab combined with lenalidomide. Patients with double- or triple-hit lymphoma or primary refractory DLBCL were excluded from the study. Of the 80 patients that received both tafasitamab plus lenalidomide, 60% had an objective response, and a complete response (CR) was seen in 43% of patients. Neutropenia occurred frequently, with 48% developing grade 3 or higher neutropenia and 12% developing febrile neutropenia. Serious adverse events included pneumonia in 6%, pulmonary embolism in 4%, bronchitis in 2%, atrial fibrillation in 2%, and congestive heart failure in 2% [21]. Based on the results of this phase 2 study, the FDA granted approval for the combination of tafasitamab and lenalidomide in r/r DLBCL.

2.3 Magrolimab

The first-in-class CD47-directed monoclonal antibody magrolimab has demonstrated efficacy in patients with NHL in early phase clinical investigation. Magrolimab works by disrupting the interaction between CD47 on the surface of tumor cells with signal regulatory protein alpha (SIRPα) on macrophages, unmasking pro-phagocytic signals on the surface of cancer cells, leading to their destruction. In a phase 1b/2 trial, magrolimab was combined with rituximab in r/r DLBCL and follicular lymphoma, since magrolimab augmented antibody-dependent cytotoxicity of rituximab by promoting enhanced phagocytosis in preclinical studies [22, 23]. Updated results from the 1b/2 trial were reported and included primary refractory or r/r DLBCL treated with two or more prior lines of therapy ineligible for CAR T cell treatment. Grade 3 or higher toxicity was uncommon with 15% grade 3 anemia occurring most frequently, an expected on-target transient first-dose effect. The ORR was 39%, and the CR rate was 20% ($n = 46$). The extended follow-up of patients from the phase 1b trial demonstrated ongoing durable responses beyond 20 months of follow-up [24, 25].

2.4 Monoclonal Antibodies Summary

Since the advent of rituximab, monoclonal antibodies have not dramatically changed the treatment landscape of DLBCL. In terms of logical sequencing, rituximab maintains its foothold in front-line combination therapy and in rational combination therapies in the r/r setting when CD20 expression is present. Obinutuzumab has not improved outcomes in DLBCL; therefore, a clear role for the drug in DLBCL is yet to be established. The CD19 monoclonal antibody tafasitamab has a demonstrable role in the r/r setting, but its utility is unclear in patients with high-risk disease including double- and triple-hit and primary refractory disease who were excluded from the study. Despite this fact, the tafasitamab/lenalidomide combination can be considered in patients unfit for ASCT and CAR T cell therapy or in

patients relapsed after these therapies with ongoing CD19 expression.

3 Antibody–Drug Conjugates (ADCs)

ADCs are biopharmaceutical compounds consisting of a chemotherapeutic agent linked to an antibody capable of targeted delivery of the payload to cells expressing the target protein. ADCs currently in use for DLBCL target a range of antigens and use a variety of different payloads.

3.1 Polatuzumab Vedotin

Monomethyl auristatin E (MMAE) covalently bound to a monoclonal anti-CD79b antibody comprises the ADC polatuzumab vedotin (PoV). MMAE works by binding to tubulin inside the cell, thereby preventing mitosis. Unbound, it carries a significant toxicity profile. However, when covalently bound to the polatuzumab antibody, it is directed to cells containing only the CD79b subunit of the B cell receptor, which is expressed ubiquitously on the surface of human B cells and lymphomatous B cells. In r/r DLBCL, the combination of PoV with rituximab or obinutuzumab in a phase 2 trial resulted in an ORR of 54% and a CR rate of 21% [26]. In a phase 2 study, a randomized cohort compared PoV combined with bendamustine and rituximab (BR) against BR alone, with the primary endpoint being CR at the end of six cycles of therapy. In a group of 40 patients with r/r DLBCL, the best ORR was 70% and the best CR rate was 57.5% in the PoV-BR group, compared to 32.5% and 20%, respectively, in the BR group. In addition, in the PoV-BR group, median OS and PFS were significantly longer than in the BR group (12.4 and 4.7 months vs 9.5 and 3.7 months, respectively). Toxicity in the PoV group included higher peripheral neuropathy and hematologic toxicity rates [27]. Based on these results, PoV was granted accelerated approval by the FDA in r/r DLBCL. Ongoing trials evaluating the combination of polatuzumab with chemotherapy include the POLARIX trial (NCT03274492), a phase 3 randomized trial comparing rituximab, cyclophosphamide, doxorubicin, prednisone (R-CHP) combined with polatuzumab with R-CHOP in the front-line setting, as well as the PolaR-ICE trial, a phase 2 trial evaluating the efficacy of the combination of polatuzumab with rituximab, ifosfamide, carboplatin, etoposide (R-ICE) as first salvage therapy in r/r DLBCL (NCT04665765). In addition, the efficacy data from the phase 1b/2 trial combining PoV and rituximab with venetoclax demonstrated an investigator-assessed CR rate of 31% and a best ORR of 65%, with a median PFS of 4.4 months and an OS of 11 months. The most common grade 3 or higher adverse events were neutropenia (53%), infections (16%), and anemia (11%) [28].

3.2 Brentuximab Vedotin

Brentuximab vedotin (BV) is similar to PoV in that it carries the same chemotherapeutic payload, MMAE. In the case of BV, however, the covalently bound monoclonal antibody is directed instead against CD30. BV is well known for its efficacy in treating Hodgkin's lymphoma, but it has been studied in DLBCL as well. A phase 2 study was performed in NHL with a pre-planned subset of 49 patients with r/r DLBCL with variable CD30 expression levels. ORR was 44%, with a CR rate of 17%. Although there was no correlation between response and CD30 expression, all patients who responded had quantifiable CD30 expression by computer-assisted digital image analysis of immunohistochemistry. Toxicity was largely mild and self-limited, with grade 3/4 fatigue, neutropenia, and nausea occurring most frequently. A small cohort of 15 patients were treated in the study with the combination of rituximab and BV, with similar efficacy to BV alone and a favorable safety profile [29]. In addition, a phase 1 study evaluated the safety of the combination of BV with lenalidomide. The study enrolled both CD30-positive and CD30-negative patients and both germinal center B-cell type (GCB) and non-GCB subtypes of r/r DLBCL. The ORR was 53%, with a CR rate of 41%, among 17 evaluable patients [30]. There is an ongoing phase 3 placebo-controlled, double-blinded, multicenter trial comparing rituximab, lenalidomide, and BV with rituximab, lenalidomide, and placebo in patients with two or more prior lines of therapy that are ineligible or have declined stem cell transplant or CAR T cell therapy (NCT04404283).

3.3 CD22 ADCs

The clinical utility of CD22 ADCs has not been realized in practice. For example, pinatuzumab vedotin (PiV) is an anti-CD22 ADC similar to BV and PoV in that its payload is also MMAE. The combination of PiV with rituximab was tested in the phase 2 ROMULUS study in patients with r/r DLBCL, with promising response rates (ORR 57%, CR 24%); however, the high rate of grade 5 adverse events (21%), more than half of which were infections, has limited further use of this drug [26]. Inotuzumab ozogamicin (InO) is a second CD22-targeted ADC that showed promising efficacy in early trials [31, 32]. Unfortunately, these results could not be replicated in subsequent studies and interest waned in this therapy when serious infections and hepatic toxicity after ASCT occurred in a significant proportion of patients [33]. Despite the efficacy seen in some of the early phase

Table 1 List of major trials using immunotherapy agents in r/r DLBCL

Therapy category	Name of agent	Target	Trial	Response	Survival	Major toxicities	FDA approval/trial number
Monoclonal antibodies	Obinutuzumab	CD20	GOYA (G-CHOP vs R-CHOP)	ORR 77.6%, CR 59.1%	5Y PFS 63.8%, 5Y OS 77.0%	75.1% G3-5 AEs	No PFS improvement over R-CHOP: not approved
			R/R single agent	ORR 37%			Not approved
	Tafasitamab	CD19	R/R single agent	ORR 26%			Not approved
			L-MIND (R/R combined with lenalidomide)	ORR 60%, CR 43%		12% febrile neutropenia, 6% pneumonia, 4% PE, 2% Afib	FDA approved in r/r DLBCL beyond 2nd line
	Magrolimab	CD47	R/R combined with rituximab	ORR 39%, CR 20%		15% ≥ G3 SAEs	Not approved
ADCs	Polatuzumab vedotin	CD79b	R/R combined with rituximab or obinutuzumab	ORR 54%, CR 21%			Not approved
			R/R combined with BR vs BR	ORR 70%, CR 57.5%	PFS 4.7 mos, OS 12.4 mos	Higher peripheral neuropathy and hematologic toxicity compared to BR	FDA approved in r/r DLBCL beyond 2nd line
			R/R combined with rituximab and venetoclax	ORR 65%, CR 31%	PFS 4.4 mos, OS 11 mos	≥ G3 neutropenia 53%, infections 16%, anemia 11%	Not approved
	Brentuximab vedotin	CD30	R/R single agent	ORR 44%, CR 17%		≥ G3 fatigue, neutropenia, nausea most common	Not approved
			R/R combined with lenalidomide	ORR 53%, CR 41%			Not approved
	Pinatuzumab vedotin	CD22	ROMULUS (R/R combined with rituximab)	ORR 57%, CR 24%		G5 toxicity 21%	Not approved

Table 1 (continued)

Therapy category	Name of agent	Target	Trial	Response	Survival	Major toxicities	FDA approval/trial number
Bispecific antibodies	Blinatumomab	CD19	R/R single agent	ORR 43%, CR 19%		17% discontinued therapy due to neurotoxicity	Not approved
			R/R second salvage followed by ASCT	ORR 37%, CR 22%		≥ G3 AEs 71%, ≥ G3 neurotoxicity 24%	Not approved
	Mosunetuzumab	CD20	R/R single agent	ORR 33%, CR 21%		28.4% CRS mainly grade 1	Not approved
	Odronextamab	CD20	R/R single agent	ORR 33%, CR 23.8%		≥ G3 CRS 7%, ≥ G3 neurotoxicity 2.3%	Not approved
	Glofitamab	CD20	R/R with obinutuzumab pre-treatment	ORR 50%, CR 29.2%		CRS, pyrexia, hematologic toxicity, but none leading to cessation of treatment	Not approved
	Epcoritamab	CD20	R/R single agent	ORR 56%, CR 44%		CRS, pyrexia, hematologic toxicity, but none leading to cessation of treatment	Not approved
CAR T	Axicabtagene ciloleucel	CD19	ZUMA-1 R/R after 2 lines	ORR 83%, CR 59%	PFS 5.9 mos, OS NR	≥ G3 AEs 48%, ≥ G3 CRS 11%, ≥ G3 neurotoxicity 35%	FDA approved in r/r DLBCL 3rd line
	Tisagenlecleucel	CD19	R/R after 2 lines	ORR 52%, CR 40%		≥ G3 CRS 22%, ≥ G3 neurotoxicity 14%	FDA approved in r/r DLBCL 3rd line
	Lisocabtagene maraleucel	CD19	TRANSCEND – R/R after 2 lines	ORR 73%, CR 53%		≥ G3 CRS 2%, ≥ G3 neurotoxicity 10%	FDA approved in r/r DLBCL 3rd line
	ALLO-501/ALLO-647	CD19/CD52	R/R after 2 lines, ALLO-647 is part of lymphodepletion	ORR 78%, CR 33%		22% CRS none grade 3 or higher, no ICANS	Not approved
	AUTO3	CD19/CD22	R/R in combination with pembrolizumab	ORR 69%, CR 52%		CRS 0%, neurotoxicity 9%	Not approved
	CAR22	CD22	R/R after CD19 CAR T	ORR 100%, CR 100%		No grade 3 or higher CRS or ICANS	Not approved

ADC antibody drug conjugate, *AE* adverse event, *Afib* atrial fibrillation, *ASCT* autologous stem cell transplantation, *BR* bendamustine and rituximab, *CAR* chimeric antigen receptor, *CAR T* CAR T cell therapy, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone, *CR* complete response, *CRS* cytokine release syndrome, *DLBCL* diffuse large B cell lymphoma, *FDA* Food and Drug Administration, *G* grade, *G-CHOP* obinutuzumab, cyclophosphamide, doxorubicin, vincristine, prednisone, *ICANS* immune effector cell associated neurologic syndrome, *mos* months, *ORR* overall response rate, *OS* overall survival, *PE* pulmonary embolism, *PFS* progression-free survival, *R-CHOP* rituximab + CHOP, *R/R* relapsed/refractory, *SAE* serious adverse event, *5Y* 5 year

Table 2 List of major ongoing trials of immunotherapy agents in r/r DLBCL

Therapy category	Name of agent	Target	Trial	Trial ID
ADC	PoV	CD79b	POLARIX—PoV-CHP vs R-CHOP in frontline DLBCL	NCT03274492
			PolaR-ICE—PoV + R-ICE as first salvage in r/r DLBCL	NCT04665765
	BV	CD30	Rituximab, lenalidomide, and BV vs rituximab, lenalidomide	NCT04404283
Bispecific antibodies	Odronextamab	CD20	r/r beyond 2nd line without prior CAR T or BiTE	NCT03888105
	Epcoritamab	CD20	r/r beyond 2nd line single agent	NCT03625037
CAR T	Axi-cel	CD19	ZUMA-7—axi-cel vs SOC 1st salvage	NCT03391466
	Tisa-cel	CD19	BELINDA—tisa-cel vs SOC 1st salvage	NCT03570892
	Liso-cel	CD19	TRANSFORM—liso-cel vs SOC 1st salvage	NCT03575351
	PBCAR20A	CD20	r/r beyond 2nd line single agent	NCT04030195
	MB-106	CD20	r/r beyond 2nd line single agent	NCT03277729

ADC antibody drug conjugate, *axi-cel* axicabtagene ciloleucel, *BiTE* bispecific T cell engager, *BV* brentuximab vedotin, *CAR* chimeric antigen receptor, *CAR T* CAR T cell therapy, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone, *CHP* cyclophosphamide, doxorubicin, prednisone, *DLBCL* diffuse large B cell lymphoma, *liso-cel* lisocabtagene maraleucel, *PoV* polatuzumab vedotin, *R-CHOP* rituximab + CHOP, *R-ICE* rituximab, ifosfamide, carboplatin, etoposide, *r/r* relapsed and/or refractory, *SOC* standard of care, *tisa-cel* tisagenlecleucel

trials, when the combination of InO with rituximab was tested in a randomized phase 3 trial against the combination of rituximab with bendamustine or gemcitabine, there was no difference between the arms in ORR, PFS, or OS [34]. More recently, Trph-222, a CD22 ADC with a novel linker joining the antibody to the anti-mitotic agent maytansine was evaluated in a phase 1 study, with one patient with r/r DLBCL having a CR out of eight evaluable patients [35].

3.4 Loncastuximab Tesirine

Loncastuximab tesirine (LoT; ADCT-402) is a CD19 ADC that has shown efficacy in DLBCL. It contains a CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine dimer toxin, which acts by binding to the minor groove of DNA, leading to DNA cross-linking that is resistant to DNA repair mechanisms. LoT was tested in a phase 1 dose-escalation and dose-expansion study in r/r NHL. The cohort of 137 patients with DLBCL experienced a 42.3% ORR and a 23.4% CR rate, with a median duration of response of 4.5 months. Hematologic toxicity along with fatigue, nausea, edema, and liver enzyme abnormalities were the most common treatment-emergent adverse events noted [36]. In addition, preliminary results of an open-label, single-arm, phase 2 study of this drug were reported for patients with DLBCL r/r to two or more lines of prior therapy ($n = 145$) with at least 6 months of follow-up since starting treatment. Among evaluable patients, the ORR was 48.3% and the CR rate was 24.1%, with a median duration of response of 10.3 months. Importantly, response rates were comparable among patients with high-risk disease [37, 38]. A phase 1/2 trial evaluating the safety and efficacy of the combination of LoT with ibrutinib in patients with r/r DLBCL (NCT03684694) is ongoing.

3.5 ADC Summary

The ADC with the most robust data is PoV, and there are several treatment niches where it can potentially be utilized. Possibilities include using bendamustine, rituximab, polatuzumab vedotin (BR-Pola) as third-line salvage, and there is potential for its use as a bridging agent while awaiting CAR T cell production [39]. A logical role for BR-Pola is following CAR T cell therapy failure. BV may have a role in r/r CD30-positive disease, and its role in combination therapy is actively under investigation. Unfortunately, CD22-directed ADCs have been largely disappointing, while the CD19 ADC LoT may end up having clinical utility as a single agent or in combination in patients who are not candidates for or who have progressed after cellular therapies.

4 Bispecific T Cell Engager (BiTE) Antibodies

Bispecific T cell engager (BiTE) antibodies are engineered antibody molecules with dual specificity to target both an antigen on the tumor as well as an antigen on immune cells. The result is activation of an immune response against the tumor due to close proximity of the immune cells with the tumor cells. Typical BiTE antibodies consist of a tumor antigen target as well as a CD3 target, which is expressed on T cells.

4.1 Blinatumomab

The first FDA-approved BiTE was blinatumomab, which is a dual specificity antibody binding both to CD19 on target B cells as well as the CD3e subunit of the T cell receptor. It is currently approved for use in acute lymphoblastic

leukemia and has been studied in DLBCL. In a phase 2 study in r/r DLBCL, patients were treated with either an escalating dose or a flat dose of 112 ug/day. The ORR was 43%, with 19% CR. Significant rates of neurotoxicity were seen despite dexamethasone prophylaxis, with 17% of discontinuation of therapy being due to neurotoxicity events [40]. Similar results were seen in the phase 2 portion of a phase 2/3 trial investigating blinatumomab as second salvage in r/r DLBCL, with an ORR of 37%, a 22% CR, and 20% of patients going on to receive ASCT. Toxicity included grade 3 or higher adverse events in 71% of patients, with 24% of patients experiencing grade 3 neurologic events [41]. A pooled analysis of phase 1 and 2 trials of blinatumomab in r/r DLBCL indicated that patients achieving CR had durable responses, with 62.2% of patients remaining in remission at 21 months [42]. In a phase 1 study combining blinatumomab with lenalidomide in r/r NHL, data on 18 patients treated with this combination were reported, including seven with r/r DLBCL [43]. Of those treated with the combination, the ORR was 83%, with a 50% CR rate and a median PFS of 8.3 months. The most common grade 3/3 adverse events were lymphopenia and electrolyte abnormalities, with one patient experiencing grade 3 neurotoxicity and no grade 3/4 cytokine release syndrome (CRS).

4.2 Mosunetuzumab

Mosunetuzumab is a full-length, fully humanized IgG1 BiTE antibody directed against CD20 and CD3. The drug is being evaluated in an ongoing phase 1/1b trial of r/r NHL patients, 55 of whom had DLBCL. The ORR was 33% among r/r DLBCL, and the CR rate was 21%. The most common adverse event was CRS (28.4%), usually mild, with only 1.4% above grade 2. In contrast to blinatumomab, neurotoxicity was not seen. Notably, all patients achieving CR remained in remission at the time of reporting of the study [44]. The follow-up report of patients in group B of the same trial, which involved ramp-up dosing, included 87 patients with DLBCL who achieved a 34.7% ORR, with a CR rate of 18.6%. Dose escalation was ongoing as the maximum tolerated dose had not yet been reached. Among patients previously treated with CAR T cell therapy, two out of seven patients with r/r DLBCL had CR with evidence of expansion of the previously administered CAR T cell product [45].

4.3 Odronextamab

Odronextamab (REGN1979) is a hinge-stabilized, fully human IgG4 bispecific antibody also targeting CD20 and CD3. In a phase 1 dose-escalation and early dose expansion phase trial, patients with r/r NHL were treated with the drug, including 71 patients with DLBCL. Among ten patients with r/r DLBCL not previously treated with CAR T cells, who were treated at the highest dose level of odronextamab, the ORR and CR rate was 60%, with a median duration of response of 10.3 months. In DLBCL patients refractory to prior CAR T cell therapy, the ORR rate dropped to 33% and the CR rate was 23.8%. Overall toxicity included pyrexia, CRS, and chills most commonly, with just over 7% of patients having grade 3 or higher CRS and 2.3% of patients having neurologic toxicity [46]. A phase 2 study of odronextamab in r/r DLBCL is currently ongoing and includes patients treated with more than two prior lines of therapy, but does not allow prior CAR T cell treatment or treatment with other CD20 bispecific antibody (NCT03888105).

4.4 Glofitamab

Glofitamab (RG6026) is a T cell-engaging, bispecific, full-length antibody with a 2:1 molecular confirmation that leads to bivalent binding of CD20 and monovalent binding of CD3. Preclinical testing of potency indicates it may be more potent than bispecific antibodies with 1:1 formats. Preliminary data from a phase 1/1b dose-escalation and dose-expansion trial of glofitamab with obinutuzumab pretreatment for the mitigation of CRS demonstrated promising results in r/r aggressive B cell NHL. In the 24 patients evaluated, the ORR was 50%, with a CR rate of 29.2%. The most common adverse events included CRS, pyrexia, hematologic toxicity, and hypophosphatemia, although no adverse event led to treatment discontinuation [47].

4.5 Epcoritamab

The CD20 × CD3 BiTE epcoritamab (GEN3013) was specifically formulated to be given subcutaneously. Preliminary results from a phase 1/2 study in r/r NHL demonstrate a favorable toxicity profile, consistent with other CD20 BiTEs, with pyrexia, fatigue, and CRS as the most commonly occurring adverse events. There were no dose-limiting toxicities reported. Of the nine patients with DLBCL or high-grade B cell lymphoma that were evaluable at the time the study results were reported, 56% had achieved a response, with 44% achieving a CR. The phase 2 portion of the trial is ongoing (NCT03625037) [48].

4.6 BiTE Summary

With the success of rituximab, it is not surprising that many of the CD20 bispecific antibodies have shown efficacy. Mosunetuzumab has the most robust clinical data so far, with other agents showing promising efficacy as well. The efficacy of these agents either after failure of rituximab and/or failure of cellular therapy gives hope for patients with an otherwise very challenging disease to treat. It will be

important to also evaluate the potential for these agents to improve outcomes in earlier lines of therapy, and these investigations are ongoing. Currently, these agents remain under investigation and find their role in the timing of immunotherapy for DLBCL after failure of CAR T cells; however, this may change with the results of ongoing trials.

5 Chimeric Antigen Receptor (CAR) T cell Therapy

CAR T cell therapy involves genetically modifying T cells with a CAR construct that directs the T cell to a specific target and then enhances the T cell response, T cell proliferation, and immune response. A typical CAR construct contains the extracellular antigen recognition domain, the hinge region, transmembrane domain, and the intracellular T cell stimulatory domain and co-stimulatory domain. To date, three CAR T cell therapies have been approved by the FDA in r/r DLBCL, axi-cel, tisa-cel, and liso-cel, all of which are autologous products that target CD19 and will be discussed in more detail below. The efficacy of these agents in r/r DLBCL has revolutionized treatment of a disease that was largely incurable previously. In fact, in the SCHOLAR-1 study, retrospective analysis of patients with r/r DLBCL demonstrated that after second-line therapy, the ORR was 26% to the next line of therapy, with a median OS of 6.3 months [49]. In stark contrast, response rates for the FDA-approved CAR T cell products ranged from 50% to 80%, with a median OS not being reached.

5.1 Axicabtagene Ciloleucel

Axicabtagene ciloleucel (axi-cel or Yescarta) is a CD19-directed, autologous, CAR T cell product with a CD28 costimulatory domain approved for the treatment of r/r large B cell lymphoma. Of 119 patients enrolled on the pivotal ZUMA-1 trial across the phase 1 and 2 portions, 108 received axi-cel. Of the 101 patients assessable in the phase 2 portion, the median follow-up was 27.1 months, with an ORR of 83% and a CR of 59%. Response rates were similar across subgroups including transformed follicular lymphoma and primary mediastinal B cell lymphoma (PMBCL). The median duration of response was 11.1 months, the median PFS was 5.9 months, and the median OS was not reached. Forty-eight percent of patients had grade 3 or higher adverse events, with grade 3 or higher CRS or neurotoxicity occurring in 11% and 35% of patients, respectively. Among patients with double-expressor and high-grade B cell lymphoma with myc and bcl2 and/or bcl6 translocations, the ORR was 91%, with a CR rate of 70% [11, 50]. Several clinical trials utilizing axi-cel are ongoing, including ZUMA-6, a phase 1/2 trial involving treatment of patients with r/r DLBCL with axi-cel combined with the anti-programmed cell death ligand 1 (anti-PD-L1) antibody atezolizumab. Results of the phase 1 cohort 3 and phase 2 portions were pooled as they used the same dosing schedule and showed an ORR of 75%, with a CR rate of 46%. Grade 3 or higher CRS occurred in 4%, while G3 or higher neurologic events occurred in 29% [51]. In addition, ZUMA-7 is a randomized phase 3 trial comparing axi-cel therapy to SOC in patients with r/r DLBCL as first salvage treatment. In the SOC arm, patients receive investigator's choice of multi-agent chemo-immunotherapy followed by ASCT for those with a response to treatment (NCT03391466). Finally, ZUMA-12, an open-label, phase 2 study is investigating the role of axi-cel in the front-line setting in patients with high-risk large B cell lymphoma, including those with double- or triple-hit lymphoma, an international prognostic index (IPI) score of 3 or greater, or persistent or progressive disease after two cycles of anthracycline-containing chemotherapy. The primary endpoint is investigator-assessed CR. As of the interim report, 31 patients were enrolled and treated and 15 had been treated with axi-cel. The investigator-assessed ORR was 93%, with a CR of 80%, while in the 12 patients with centrally confirmed high-risk DLBCL who received axi-cel, the ORR was 92% and the CR rate was 75%. Of note, CAR T cell peaks were higher in ZUMA-12 than ZUMA-1, while the disease burden tended to be lower, underscoring the potential for changes in the pharmacology of CAR T cell therapies based on burden of prior therapies [52].

5.2 Tisagenlecleucel

Tisagenlecleucel (tisa-cel or Kymriah) is another CD19-directed, autologous, CAR T cell product, but instead of a CD28 costimulatory domain, it contains a 4-1BB costimulatory domain. In the phase 2 multicenter study, 93 patients with r/r DLBCL received an infusion of the CAR T cell product. The best ORR was 52%, with a CR rate of 40%. The most common adverse events at grade 3 or higher included hematologic toxicity, infections, and febrile neutropenia. Adverse events of special interest included CRS that occurred in 22% of patients and neurologic events that occurred in 14% [53]. Similar to ZUMA-7 with axi-cel, the BELINDA trial is a randomized phase 3 trial comparing the efficacy, safety, and tolerability of tisa-cel to SOC in adult patients with r/r DLBCL for first salvage. This trial includes DLBCL as well as follicular lymphoma grade 3B, PMBCL, anaplastic lymphoma kinase-positive large B cell lymphoma, double-hit, and DLBCL transformed from other low-grade lymphomas (NCT03570892).

5.3 Lisocabtagene Maraleucel

Lisocabtagene maraleucel (liso-cel or Breyanzi) is the third FDA-approved, autologous CAR T cell product that targets CD19, and it also contains a 4-1BB costimulatory domain. In the TRANSCEND trial, patients with r/r DLBCL were enrolled, including high-risk subgroups with double-hit and triple-hit lymphoma, DLBCL transformed from low-grade lymphoma, as well as PMBCL and grade 3B follicular lymphoma if they had received two or more prior treatments. Patients with secondary central nervous system (CNS) lymphoma were also eligible. Of the 344 patients who underwent leukapheresis, 269 received one dose of liso-cel. Patients were dosed with one of three dose levels, with the final recommended target dose being 100×10^6 CAR T cells. The ORR was 73% and CR rate was 53%. Interestingly, among the 3% of patients with secondary CNS involvement enrolled in the trial, the CR rate was 50%. The most common grade 3 toxicity was hematologic, with grade 3 neutropenia occurring in 60% of patients. Grade 3 CRS occurred in 2% of patients, and grade 3 neurologic events occurred in 10%. In addition, the TRANSFORM trial, a randomized phase 3 trial, is actively enrolling patients. Transplant-eligible patients with high-risk aggressive B cell NHL r/r to one prior line of therapy are randomized to receive liso-cel or SOC with salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell rescue (NCT03575351).

5.4 Novel CAR T Cell Therapies Under Investigation

PBCAR0191 is an allogeneic CAR T cell product directed against CD19, with data presented from the phase 1 trial including three patients with NHL, two of which had objective response at dose level 1. Patients had at least two prior lines of therapy and had to be considered for SOC CAR T cell therapy. Minimal toxicity was noted in patients receiving therapy [54].

ALLO-501 is another allogeneic CD19-directed CAR T cell product with some early clinical data in NHL. The phase 1 study combined the off-the-shelf CAR T cell product with ALLO-647, an anti-CD52 antibody, during lymphodepletion. Twelve patients with r/r NHL with more than two prior lines of therapy were enrolled, and of those, nine patients received ALLO-501. The ORR was 78%, with a 33% CR rate. Hematologic toxicity was the most common grade 3 or higher toxicity, with 55.6% of patients developing grade 3 or higher neutropenia. Twenty-two percent of patients developed CRS, none grade 3 or higher, and one patient developed grade 1 neurotoxicity that resolved without treatment [55].

PBCAR20A is an allogeneic product directed against CD20 with an early phase clinical trial ongoing in r/r NHL (NCT04030195). Inclusion criteria include r/r B cell NHL with CD20 expression. DLBCL patients must have had at least two prior lines of therapy and must have been considered for SOC CAR T cell therapy.

MB-106 is another off-the-shelf CD20-directed CAR T cell product in early phase trial investigation. The phase 1/2 clinical trial is aimed at evaluating the safety and efficacy of this agent in patients with r/r B cell NHL (NCT03277729).

In contrast to these allogeneic products, AUTO3 is a bispecific CAR T cell product directed against CD19 and CD22. A phase 1/2 clinical trial is ongoing, investigating the combination of this allogeneic product with pembrolizumab in r/r DLBCL, including transformed DLBCL. Thirty-three patients were treated with AUTO3, and 29 were evaluable for efficacy, with an ORR of 69% and a CR rate of 52%. The most common adverse events greater than grade 3 were hematologic. CRS was 0%, while neurotoxicity was 9%, and was felt to be possibly confounded by other ongoing events such as sepsis [56].

Another autologous product, CAR22, is directed against the CD22 protein. In three patients with DLBCL treated in a phase 1 trial, all of whom were refractory to a prior CD19-directed CAR T cell product, all achieved response by day 28, with one patient achieving CR and two achieving partial response (PR). Importantly, all patients converted to a CR and remained in remission at the time of presentation. CRS was seen in 88% of patients, including those treated for B cell acute lymphoblastic leukemia (ALL); however, all CRS was grade 1 or 2. There were no cases of immune effector cell associated neurologic syndrome (ICANS) [57].

5.5 CAR T Cell Therapy Summary

The choice among FDA-approved CAR T cell products for the treatment of r/r DLBCL can be challenging given the overlap in inclusion and exclusion criteria, the excellent efficacy and toxicity profiles seen across trials, and the lack of head-to-head comparisons of these agents. Nevertheless, there are unique characteristics to the various agents that may help the decision-making process in certain cases. For example, liso-cel was the only agent to demonstrate activity in patients with secondary CNS lymphoma, as CNS lymphoma was an exclusion criteria from the other two trials. In addition, inclusion criteria for the clinical trial testing tisa-cel allowed patients with broader organ function. Attempts at teasing out which choice may be better have been challenging, and it may be reasonable to make a choice based on familiarity with a specific product at a given institution or individual experiences with product manufacturing success rates. That being said, there is some evidence that liso-cel and tisa-cel may have more favorable severe toxicity rates, which may allow for easier outpatient administration, but given a lack of head-to-head comparisons, it is difficult to

draw conclusions [58]. Beyond the FDA-approved therapies, allogeneic CAR T cell products appear efficacious and may have a role in patients unable to await the manufacturing times associated with autologous products, and novel targets may play a role in CD19 CAR T cell refractory disease.

6 Conclusion

In recent years, there have been several advances in the field of immunotherapy for r/r DLBCL. CAR T cells have revolutionized the treatment of r/r DLBCL and provided durable responses in a proportion of patients who would otherwise have no treatment options. In fact, salvage treatment beyond second line was typically not considered curative unless followed by consolidation with allogeneic hematopoietic cell transplantation (alloHCT) [59]. Multiple retrospective reviews evaluating outcomes of patients with r/r DLBCL treated with alloHCT demonstrate evidence for long-term survival, with 5-year OS reported between 20% and 40%; however, there are significant rates of non-relapse mortality, ranging from 20% to 50% in some studies [59–61]. Given the demonstrable efficacy, durability of response, and comparably mild toxicity of CAR T cell therapy, CAR T cells have become the established third-line treatment for DLBCL and may become part of earlier therapy lines, pending the results of ongoing studies. Other recently approved immunotherapies for r/r DLBCL include tafasitamab in combination with lenalidomide and PoV combined with BR. Ongoing studies will clarify the ultimate role of these novel agents, but currently they can be used after CAR T cell therapy failure, for patients who are transplant or CAR T cell therapy ineligible, or may be considered as a bridge to CAR T cell therapy—although the data supporting the latter approach are lacking. BiTE antibodies and novel CAR T cell therapies have demonstrated early efficacy and have the promise to become effective therapeutic options for r/r DLBCL patients, and further complicate decision-making for these patients. Given the biologic heterogeneity and poor outcomes historically observed in patients with r/r DLBCL, more therapy choices would be a welcome problem.

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