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Review

ABCs of ADCs in management of relapsed/refractory diffuse large B-cell lymphoma

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ABSTRACT

In the past 5 years, 3 chimeric antigen receptor (CAR) T-cell therapies, 2 antibody-drug conjugates (ADCs), 1 CD19-directed monoclonal antibody, and 1 exportin-1 inhibitor have been approved by the Food and Drug Administration for patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL). The noncellular therapies received accelerated approval based on the overall response rate in clinical trials that differ in multiple aspects of the patient populations enrolled, including age, performance status, prior lines of therapy, and inclusion of patients with primary refractory DLBCL, transformed lymphoma, or high-grade B-cell lymphoma with rearrangements of *MYC* and *BCL2* and/or *BCL6*. ADCs approved for DLBCL differ in target antigen, antibody structure, linker, and cytotoxin, which results in a different safety and efficacy profile. Here, we comprehensively review the current knowledge of recently approved and emerging strategies for the management of R/R DLBCL with a focus on ADCs.

1. Introduction

Non-Hodgkin lymphoma (NHL) is the seventh leading type of cancer, accounting for approximately 4% to 5% of new cancer cases and 3% to 4% of cancer-related deaths [1]. The American Cancer Society estimates 81,560 patients were diagnosed with NHL in 2020, with an estimated 20,720 deaths [2]. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, comprising approximately 32% of NHL cases diagnosed in the US [1]. The 5-year relative survival for DLBCL based on Surveillance, Epidemiology, and End Results (SEER) program data from 2011 to 2017 is 63.9% [3]. In the last 5 years, 7 new therapies with diverse therapeutic targets have been granted regulatory approval by the FDA for the management of R/R DLBCL (Table 1). These novel strategies for the treatment of R/R DLBCL target cell surface markers, cellular pathways, and the tumor microenvironment.

Among the noncellular therapies recently approved by the FDA for R/R DLBCL, antibody-drug conjugates (ADCs) offer a mechanism to enhance the therapeutic index over traditional chemotherapy by delivery of a cytotoxin to tumor cells via a targeted antibody. In 2019, polatuzumab vedotin, an ADC that delivers the cytotoxin monomethyl auristatin E (MMAE) by targeting CD79b, was approved in the third-line setting in combination with bendamustine and rituximab (BR) [4]. Tafasitamab, a monoclonal antibody targeting CD19 in combination with the immunomodulatory agent lenalidomide, was approved in 2020 for patients with R/R DLBCL who are not candidates for autologous stem cell transplant (ASCT) [5]. Selinexor, a selective inhibitor of the nuclear export protein exportin 1 (XPO1), received approval in 2020 for patients with R/R DLBCL after at least 2 lines of therapy [6]. Loncastuximab tesirine, a CD19-directed ADC linked to a pyrrolobenzodiazepine (PBD) dimer, an alkylating cytotoxin, was approved as monotherapy for patients with DLBCL after at least 2 prior lines of therapy in 2021 [7]. Several phase 3 randomized, controlled trials in first- and second-line DLBCL have recently been published, and axicabtagene ciloleucel (axicel) was recently approved by the FDA for adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy [8].

Aside from studies evaluating cellular therapies, few randomized controlled trials have been carried out in patients with R/R DLBCL [9]. The noncellular therapies received accelerated approval based on the overall response rate in phase 2 trials; confirmatory randomized trials are required for continued approval and confirmation of the efficacy of these recently approved noncellular therapies [4–7]. Notably, confirmatory trials were not required for continued approval of CAR T-cell therapies in third-line or later DLBCL. Given the rapidly evolving

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Table 1
Recent drug approvals in diffuse large B-cell lymphoma [97,98].

Drug	Approval date	Class	Target	Indication
Axicabtagene ciloleucel (Yescarta®)	October 18, 2017 April 1, 2022	CAR-T	CD19	Adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.
Tisagenlecleucel (Kymriah®)	May 1, 2018	CAR-T	CD19	Adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
Polatuzumab vedotin-piiq (Polivy®)	June 10, 2019	ADC	CD79b	In combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, after at least 2 prior therapies.
Selinexor (Xpovio™)	June 22, 2020	Nuclear Export Inhibitor	XPO1	Adult patients with relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy.
Tafasitamab-cxix (Monjuvi®)	July 31, 2020	mAb	CD19	In combination with lenalidomide for the treatment of adult patients with relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from low-grade lymphoma, and who are not eligible for autologous stem cell transplant.
Lisocabtagene maraleucel (Breyanzi®)	February 5, 2021	CAR-T	CD19	Adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.
Loncastuximab tesirine-lpyl (Zynlonta™)	April 23, 2021	ADC	CD19	Adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.

ADC, antibody-drug conjugate; CAR-T, chimeric antigen receptor T-cell immunotherapy; DLBCL, diffuse large B-cell lymphoma; mAb, monoclonal antibody; XPO1, exportin 1.

landscape and lack of comparative data, minimal consensus exists on the sequencing of therapy in patients with R/R DLBCL, especially among agents with the same target (e.g., CD19). In this review, we focus on the management of R/R DLBCL and highlight the role of ADCs in the treatment paradigm.

2. First-line therapy

Randomized controlled trials established a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as the standard of care for first-line therapy of DLBCL more than 15 years ago [10,11]. Attempts to improve outcomes by intensifying therapy, consolidation with ASCT, or maintenance therapy have not improved overall survival (OS) with an acceptable toxicity profile [12,13]. Approximately 40% of patients do not have long-term remission following R-CHOP, including 9.4% of patients who develop progressive disease during treatment [11]. Outcomes of patients with R/R DLBCL differ based on the response to initial therapy, time to relapse, and opportunity to undergo ASCT. Several subgroups of patients may be at higher risk for poor outcomes with R-CHOP, including patients with primary refractory disease [14–16] and high-grade B-cell lymphoma (HGBCL) with rearrangements of *MYC* and *BCL2* and/or *BCL6* [17,18]. In some studies, patients with activated B-cell-like (ABC) DLBCL as determined by gene expression profiling also have a poorer prognosis after R-CHOP compared with patients with germinal center B-cell-like (GCB) DLBCL [19–21]. Patients who experience transformation from follicular lymphoma to DLBCL within 18 months of diagnosis, who have double-hit lymphoma/triple-hit lymphoma (DHL/THL) at transformation, and who receive R-CHOP prior to transformation as compared to R-CHOP at the time of transformation also have poor outcomes with R-CHOP [22,23].

Novel treatment strategies that can demonstrate efficacy in these subgroups are key to improving outcomes for patients with DLBCL. A recent phase 3, randomized controlled trial (POLARIX) compared polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) versus R-CHOP in 879 patients with newly diagnosed DLBCL [24]. Antibody-drug conjugates will be reviewed in greater depth in the antibody-drug conjugates section. The median age of enrolled patients was 65 years (with a range of 19 to 80), and 62% of patients in both arms had an international prognostic index (IPI) score of 3 or higher in the POLARIX trial. Similar numbers of patients receiving Pola-R-CHP or R-CHOP had the GCB subtype (55% vs. 49.7%) and DHL/THL (7.9% vs. 5.7%), respectively. After a median follow-up of 28.2 months, patients receiving Pola-R-CHP demonstrated superior PFS (HR 0.73; 95% CI, 0.57 to 0.95; $P = 0.02$), with an absolute reduction in death, progression, or relapse of 6.2%. Overall and complete responses were observed in similar numbers of

patients with an objective response rate (ORR) of 85.5% in patients receiving Pola-R-CHP and 83.8% in patients receiving R-CHOP, as well as a complete response (CR) in 78% vs. 74%, respectively; $P = 0.16$. In an exploratory subgroup analysis, younger patients, those with bulky disease, those with a lower IPI score, those with the GCB subtype of DLBCL, and those with DHL/THL did not show a clear benefit with Pola-R-CHP. No difference in the overall survival was observed between the two groups (HR 0.94; 95% CI, 0.65 to 1.37; $P = 0.75$). A higher incidence of febrile neutropenia was observed with Pola-R-CHP compared with R-CHOP (13.8% and 8.0%, respectively); however, the infection rate was similar in both groups. Peripheral neuropathy was similar in both arms as well (52.9% vs. 53.9%). A change in the standard of care treatment for first-line DLBCL may affect both the need for and the efficacy of therapies for R/R DLBCL.

3. Unmet needs in patients with R/R DLBCL

Approximately 33% to 40% of patients are refractory or relapse following initial therapy with anthracycline-containing regimens, such as R-CHOP or dose-adjusted infusional etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) [11,12]. Combination chemotherapy followed by ASCT is currently recommended for patients with chemosensitive, relapsed disease [25]. Real-world data indicate that only 13% to 46% of patients with R/R DLBCL receive an ASCT [26–32]. In addition, approximately half of patients relapse after ASCT, most often within the first 2 years [33–35]. Three chimeric antigen receptor (CAR) T-cell therapies are approved by the FDA for fit patients with R/R DLBCL in the third-line setting, and evidence from phase 3, randomized controlled trials supports a shift to the use of CAR T-cell therapies in the second-line setting in patients with early relapse or primary refractory disease [30,31]. Despite high rates of response to CAR T-cell therapy, an unmet need remains for patients with DLBCL who relapse after this therapy [36–38]. Several challenges exist with the administration of CAR T-cell therapy, including long manufacturing timelines, the need for extensive healthcare coordination, and the potential for significant treatment-related toxicity limiting the population considered eligible for therapy [39].

Treatment of elderly patients represents a unique area of unmet need in the management of DLBCL. Patients older than 65 years represent more than half of patients with DLBCL; however, only 65% of patients in this age group receive any therapy to manage DLBCL [40]. Claims-based analyses revealed that only 11% of patients over 65 years old received any second-line therapy, and a recent analysis of SEER data found that only 1.3% of patients over 65 years old received an ASCT [40,41]. Geriatric assessment is recommended by the American Society of Clinical Oncology (ASCO) Guideline for Geriatric Oncology for all patients 65 years and older [42]. A simplified geriatric assessment (sGA) in older patients with DLBCL has been developed and validated [43], which classifies patients into fit, unfit, and frail using a web-based calculator that incorporates activities of daily living (ADL), instrumental ADL, a Cumulative Illness Rating Scale for Geriatrics, and age [43]. Clinical trials assessing CAR T-cell therapy, ASCT, and immunochemotherapy in cohorts according to fitness are ongoing to discern risk and benefit in elderly patients [44].

4. Second-line therapy

Multiple clinical trials in the first-, second-, and third-line settings have the potential to change the treatment landscape of DLBCL [24,30,31]. Two phase 3, randomized controlled trials have demonstrated an improvement in EFS with CAR T-cell therapy compared with platinum-based, salvage chemotherapy, followed by ASCT in patients with early relapse or refractory DLBCL [30,31]. Preferred regimens for patients who are not candidates for cellular therapy include combinations of chemotherapy with or without monoclonal antibodies or ADCs; tafasitamab and lenalidomide is included as another recommended regimen [1]. As the standard of care changes in a given line of therapy, consideration should be given to the interpretation of clinical trials in subsequent lines of therapy as previous chemotherapy exposure will be different from the population studied. Reflection on how previous treatment may influence outcomes of subsequent therapy is warranted. For example, assessment of CD19 expression may be necessary for patients with previous exposure to CD19-directed therapy [45]. The principles for the selection of therapy will persist despite the evolving data on the management of DLBCL.

Multiple factors should be considered when sequencing therapies for R/R DLBCL. Individualized treatment decisions should be based on patient factors, including frailty assessment, comorbidities, organ function, and the ability to tolerate anticipated adverse events. Disease burden, rate of disease progression, molecular/genetic features, baseline cytopenias, risk/benefit profile of the regimen, and documented response to therapy in relevant subgroups also play a role in treatment decisions. The duration of response to prior therapy should be considered before selecting a chemotherapy-based regimen as patients with a short duration of response may be chemorefractory and unlikely to respond. Lastly, patient preferences, access to therapy, and financial considerations also factor into treatment decisions.

4.1. Cellular therapy

Eligibility for cellular therapy is based on disease characteristics, in addition to age, performance status, comorbidities, socioeconomic viability and support structure, and motivation to participate in self-care [46]. In general, optimal organ function for ASCT in patients with lymphoma includes a left ventricular ejection fraction $\geq$45%, serum creatinine less than 1.5 mg/dL, diffusing lung capacity $\geq$50%, and liver function tests less than or equal to two times the upper limit of normal [46]. The hematopoietic cell transplantation comorbidity index is a validated tool widely used to assess fitness for cellular therapy and risk of excess mortality [47]. The determination of patient fitness for CAR T-cell therapy is similar to criteria for ASCT, although there is generally no upper age limit to receive CAR T-cell therapy, and some centers use more flexible criteria for organ function [48,49].

4.1.1. Autologous stem cell transplant

ASCT has been the standard of care for patients with R/R DLBCL disease based on improvements in 5-year OS with ASCT compared with 6 cycles of dexamethasone, cisplatin, and cytarabine (53% vs. 32%, respectively; $P = 0.038$) [50]. The CORAL study randomized patients who relapsed or did not achieve a CR to primary therapy with CHOP to rituximab, dexamethasone, high-dose cytarabine, cisplatin (R-DHAP) or rituximab, ifosfamide, carboplatin, etoposide (R-ICE), followed by ASCT in patients who achieved a CR or partial response (PR) to salvage therapy [33]. Approximately 60% of patients in this study had received rituximab prior to enrollment, and 57% had relapsed or refractory disease within 12 months of initial therapy. The 3-year EFS was 31%, the 3-year PFS was 37%, and the 3-year OS was 49%. No difference was observed in patients receiving R-ICE compared with R-DHAP. Combinations of platinum-based chemotherapy are recommended for patients with an intention to proceed with ASCT [1].

Approximately half of patients relapse after ASCT, most within the first 2 years [35]. Patients who relapse after ASCT have a median post-relapse survival of only 0.7 years (95% confidence interval [CI], 0.5–0.9) [35]. In addition, large, randomized studies have demonstrated that fewer than half of transplantation-eligible patients undergo ASCT, most often because of a lack of chemosensitivity to salvage therapy [30–34]. Furthermore, real-world data suggest a minority of patients with R/R DLBCL proceed to ASCT due to advanced age, comorbid conditions, and a lack of chemosensitivity [26,27,51]. Predictors of disease progression after ASCT include positron emission tomography-positivity prior to transplant, primary refractory disease, DHL/THL, and an elevated second-line age-adjusted (saa)-IPI score [51].

4.1.2. CAR T-cell therapy

In light of the efficacy observed in the third-line setting, three trials were designed to compare the efficacy of CAR T-cell therapy to platinum-based, salvage chemotherapy followed by ASCT in patients who were refractory to first-line treatment or who had relapsed within 12 months of first-line chemoimmunotherapy, including an anti-CD20 monoclonal antibody and anthracycline-containing regimen (Table 3) [30–32]. Initial results demonstrated improved event-free survival (EFS) with lisocabtagene maraleucel (liso-cel) and axi-cel relative to standard second-line chemotherapy and transplant in primary refractory and early relapsed patients. The ZUMA-7 (axi-cel), TRANSFORM (liso-cel), and BELINDA (tisagenlecleucel, tisa-cel) studies were randomized, global, phase 3, multicenter trials of transplant-eligible patients with a primary endpoint of EFS. The definitions of EFS vary slightly among the three trials, with differences in the timing of assessment and inclusion on the start of new chemotherapy as an endpoint. The BELINDA trial enrolled a higher percentage of patients with an IPI score ≥ 2 [32]. Differences were also observed among the trials in the use of bridging therapy in the CAR T-cell therapy arms (BELINDA 83%, TRANSFORM 63%, ZUMA-7 36%) [30–32]. Importantly, in the ZUMA-7 trial, only glucocorticoids were permitted for bridging therapy [31]. In addition, the time to receipt of CAR T-cell therapy varied across trials (29 days for axi-cel and 52 days for tisa-cel). Axi-cel and liso-cel demonstrated superior EFS compared with the standard of care (HR 0.40; 95% CI, 0.31–0.51; $P < 0.001$ and HR 0.349; 95% CI, 0.229–0.530; $P < 0.0001$, respectively) [30,31]. In contrast, tisa-cel was not superior to the standard of care in the primary endpoint of EFS (HR 1.07; 95% CI, 0.82–1.40; $P = 0.61$) [32]. Follow-up among the three trials ranges from 6.2 to 24.9 months, and the overall survival data remains immature, with trends for improvement observed with both axi-cel and liso-cel [30–32]. Almost all patients in all 3 studies experienced adverse events, with rates of grade 3 or higher adverse events in over 80% in all patients [30–32]. The most recent update to the National Comprehensive Cancer Network (NCCN) guidelines supports a shift to the use of CAR T-cell therapy in the second-line for patients with early relapse (<12 months) or primary refractory disease in patients able to tolerate cellular therapy [1]. A shift to more use of CAR T-cell therapy in the second-line will create more ambiguity for how to sequence therapy in the third-line setting as robust data for the treatment of patients who relapsed after or are refractory to CAR T-cell therapy are lacking.

4.2. Non-cellular therapy

Patients are considered transplantation-ineligible if they are predicted to tolerate ASCT poorly because of age or comorbidities, if they do not show chemosensitivity to platinum-based salvage therapy, and if they have already received and relapsed after ASCT [52]. Multiple options exist for patients ineligible for or who relapsed after ASCT; however, there is no consensus on how to sequence these agents [1]. The NCCN guidelines panel recommends gemcitabine and oxaliplatin with or without rituximab, polatuzumab and bendamustine with or without rituximab, and tafasitamab plus lenalidomide as options in the second-line setting for patients ineligible for ASCT [1]. Chemotherapy-based regimens are included in the NCCN guidelines as other recommended regimens in the second-line setting.

4.2.1. Tafasitamab and lenalidomide

A phase 2, single-arm study of tafasitamab in combination with lenalidomide showed efficacy and led to regulatory approval and NCCN guideline recommendation for patients with DLBCL ineligible for ASCT in the second-line setting [1,1,53]. The L-MIND study included 80 adult patients with relapsed DLBCL who had received at least 1 but not more than 3 lines of prior therapy [53]. Patients who were eligible for ASCT or had DHL/THL, primary refractory DLBCL, or previous treatment with anti-CD19 therapy or immunomodulatory drugs such as lenalidomide were excluded. The median age of enrolled patients was 72 years (range 41–86 years) [54]. A protocol amendment resulted in inclusion of 15 (19%) patients noted to have primary refractory disease defined as relapse or progressive disease between 3 and 6 months after frontline therapy. Half of patients had received 1 prior therapy, and 49% had an IPI score of 0 to 2. The median time from diagnosis of DLBCL to treatment was 26.9 months (range 17–51 months), and 44% of patients were refractory to their most recent previous therapy. An ORR of 60% (95% CI, 48%–71%) to tafasitamab and lenalidomide was observed with a CR in 43% (95% CI, 32%–54%) of patients (Table 2). An ORR of 71% (95% CI, 48%–89%) was observed in patients with non-GCB histology, and an ORR of 50% (95% CI, 34%–66%) was observed in patients who had received 2 or more prior lines of therapy. After at least 35 months of follow-up, the median progression-free survival (PFS) was 11.6 months (95% CI, 6.3–45.7), and the median OS was 33.5 months (95% CI, 18.3–not reached) [54]. Neutropenia, anemia, and rash were the most frequent adverse events reported with tafasitamab and lenalidomide [53]. Lenalidomide was dose-reduced in 46% of patients, and 44% of patients required support with a granulocyte colony stimulating factor (G-CSF). The L-MIND study is distinct in that patients were older and lacked high-risk features such as DHL/THL, and most (93%) patients had received only 1 or 2 lines of prior therapy. The need for indefinite intravenous administration in patients achieving stable disease or better, along with cost, may dampen enthusiasm for this regimen.

5. Third-line and subsequent therapy

With each subsequent line of therapy, fewer patients receive treatment, and outcomes are progressively worse. An analysis of commercial and Medicare databases found that among patients who received first-line therapy between January 2011 and May 2017, only 17% received second-line therapy [26]. Among the second-line population, 23% received a third line, and among the third-line population, 21% received a fourth line of therapy. A retrospective analysis of the COTA database of real-world data between 2014 and 2019 found that the median OS was 7.7 months for 174 patients receiving third-line, noncellular therapy and 4.5 months for 110 patients receiving fourth-line, noncellular therapy [55]. Of 435 patients identified for the study, only 38 patients and 18 patients received cellular therapy in the third-line and fourth-line settings, respectively.

5.1. CAR T-cell therapy

Current guidelines recommend CAR T-cell therapy as an option for fit patients in the third-line setting [1]. Nearly all patients enrolled in the ZUMA-1, JULIET, and TRANSCEND-NHL-001 registrational trials had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 [36,56,57]. The age distribution of enrolled patients was significantly younger than the typical population of patients with DLBCL, with median ages for enrolled patients between 56 and 63 years. Enrolled patients were heavily pretreated with a median of 3 prior therapies [36,38,56]. More than half of the patients in the JULIET and TRANSCEND-NHL-001 trials were refractory to their last line of therapy, and three-fourths of patients in ZUMA-1 were refractory to second-line or later therapy. In addition, across all 3 trials, 13% to 15% of enrolled patients with pretreatment samples available for analysis had HGBCL. Overall response rates to CAR T-cell therapy in R/R DLBCL ranged from 52% to 82%, with CR rates of 40% to 54% (Table 3) [36,37,57]. The median PFS is approximately 3 to 7 months for commercially available CAR T-cell products to manage R/R DLBCL [36,38,56]. Progression-free survival and EFS curves plateau following CAR T-cell therapy, with approximately 40% of patients having long-term durable responses to CAR T-cell therapy [38,58,59].

It is noteworthy that results of CAR T-cell therapies reflect patients who receive CAR T-cell infusion. Only 47% of patients screened for CAR T-cell therapy in the JULIET study actually received therapy [57]; 15% of patients in TRANSCEND-NHL-001 and 9% in ZUMA-1 underwent

Table 2
Efficacy of noncellular therapies FDA-approved for R/R DLBCL [52].

Class and therapy	Target	Study	N	ORR (%) (95% CI)	CR (%) (95% CI)	Median PFS (mo) (95% CI)	Median OS (mo) (95% CI)
Antibody-drug conjugate							
Loncastuximab	CD19	LOTIS-2 [80]	145	48.3 (39.9–56.7)	24.1 (17.4–31.9)	4.9 (2.9–8.3)	9.9 (6.7–11.5)
Polatuzumab	CD79b	[72]	27	51.9 (not reported)	14.8 (not reported)	5.0 (2.3–6.8)	NR
Polatuzumab-BR vs. BR	CD79b	GO29365 [73]	80	45 vs. 17.5 (not reported)	40 vs. 17.5 (not reported)	9.5 (6.2–13.9) vs. 3.7 (2.1–4.5)	12.4 (9.0 – NE) vs. 4.7 (3.7–8.3)
Monoclonal antibody							
Tafasitamab / Lenalidomide	CD19	L-MIND [53]	80	60 (48–71)	43 (32–54)	12.1 (5.7 – NR)	NR (18.3 – NR)
Other							
Selinexor	XPO1	SADAL [67]	127	28 (20.7–37.0)	12 (6.8–18.7)	2.6 (1.9–4.0)	9.1 (6.6–15.1)

BR, Bendamustine, rituximab; CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; mo, month; NE, not evaluable; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed, refractory; XPO1, exportin-1.

Table 3
Efficacy of CAR T-cell therapy in patients receiving second- and third-line therapy for DLBCL.

	Second-line therapy						Third-line or later therapy		
	ZUMA-7 [31]		BELINDA [32]		TRANSFORM [30]		ZUMA-1 [37,56,59]	JULIET [38,57,99]	TRANSCEND [36]
	Axicabtagene ciloleucel	SOC	Tisagenlecleucel	SOC	Lisocabtagene maraleucel	SOC	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Patients enrolled, n	180	179	162	160	92	92	111	167	344
Patients infused, n (%)	170 (94.4)	64 (36)	155 (97.5)	52 (32.5)	90 (98)	42 (46)	101 (90.9)	115 (68.9)	269[b] (78.2)
Manufacturing failure, n	0	N/A	1	N/A	1	N/A	1	12	2
Best ORR % (95% CI)[c]	83 (not reported)	50 (not reported)	46.3 (38.4–54.3)	42.5 (34.7–50.6)	86 (77.0–92.3)	48[c] (37.3–58.5)	74 (not reported)	53 (43.5–62.4)	73 (66.8–78.0)
Best CR % (95% CI)	65 (not reported)	32 (not reported)	28.4 (not reported)	27.5 (not reported)	66 (55.7–75.8)	39 (29.1–49.9)	54 (not reported)	39 (not reported)	53 (46.8–59.4)
Median DOR, months (95% CI)	26.9 (13.6–NE)	8.9 (5.7–NE)	Not reported	Not reported	Not reported	Not reported	11.1 (4.2–NE)[a]	NR (10–NE)	NR (8.6–NR)
Median EFS[d], mo (95% CI)	8.3 (4.5–15.8)	2.0 (1.6–2.8)	3.0 (3.0–3.5)	3.0 (2.9–4.3)	10.1 (6.1–NR)	2.3 (2.2–4.3)	Not reported	2.8 (2.14–3.06)	Not reported
Median PFS, months (95% CI)	14.7 (5.4 – NE)	3.7 (2.9–5.3)	Not reported	Not reported	14.8 (6.6–NR)	5.7 (3.9–9.4)	5.9 (3.3–15.0)[a]	2.9 (2.3–5.2)	6.8 (3.3–14.1)
Median OS, months (95% CI)	NR	35.1 (not reported)	16.9 (11.14–NE)	15.3 (12.32–NE)	NR (15.8–NR)	16.4 (11.0–NR)	25.8 (12.8–NE)[a]	11.1 (6.6–23.9)	21.1 (13.3–NR)
OS at month 24, % (95% CI)	61 (not reported)	52 (not reported)	Not reported	Not reported	Not reported	Not reported	50.5 (40.2–59.7)	40.4 (not reported)	44.9 (36.5–52.9)

CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; NE, not estimable; NR, not reached; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; SOC, standard of care.

[a] Investigator assessed; all other data are based on assessment by independent review committee.

[b] Twenty-five patients received a nonconforming product that failed to meet specifications but was deemed safe to administer.

[c] Best response, timepoint not defined.

[d] Definitions of event-free survival (EFS) varied between trials.

leukapheresis but did not receive CAR T-cell therapy [36,37]. Patients may have disease progression while waiting to receive CAR T-cell therapy and require bridging therapy.

The potential for severe, life-threatening toxicities limits the use of CAR T-cell therapies in some patients with R/R DLBCL. Cytokine release syndrome (CRS) and neurotoxicity are common, expected adverse events associated with CAR T-cell therapy [49]. The incidence and severity of CRS and neurotoxicity vary with the CAR T-cell product. CRS is observed in 42% to 93% of patients receiving axi-cel, liso-cel, or tisa-cel with greater than grade 3 CRS in 2% to 22% of patients [36,37,57]. Neurotoxicity is less frequent; however, it is observed in 21% to 64% of patients receiving CAR T-cell therapy with greater than grade 3 neurotoxicity in 10% to 28% of patients. All 3 CAR T-cell products induce cytopenias, which may be prolonged in one-third of patients and preclude enrollment to clinical trials in those progressing after this approach [49,60]. Other toxicities include on-target B-cell depletion and hypogammaglobulinemia, which may require intravenous immunoglobulin replacement [49]. Patients with baseline cytopenias, elevated ferritin, and C-reactive protein may be at increased risk for hematologic toxicity with CAR T-cell therapy [61].

Despite the potential for cure with CAR T-cell therapy, relatively few patients receive CAR T-cell therapy for DLBCL. Based on the Center for

International Blood and Marrow Research cellular therapy registry data, fewer than 5000 patients received CAR T-cell therapy for NHL between 2016 and 2020 [62]. A survey of US-based community hematologists and oncologists in 2021 revealed that 91% of respondents had referred at least 1 patient for CAR T-cell therapy; however, only 18% of respondents had referred more than 3 patients [63]. In addition, 16% of respondents indicated none of the patients they referred ultimately received CAR T-cell therapy, suggesting that barriers remain for patients to receive this therapy. Barriers to CAR T-cell therapy are related to access to therapy, high cost of therapy, inadequate reimbursement, and the potential for significant toxicity [39,63–65]. Patients need to be referred to a CAR T-cell center, which may have a slow intake process, or there may be no CAR T-cell facility in the geographic vicinity. Subsequent delays may be related to delays in insurance approval and the need to manufacture a patient-specific product [39]. Patients also need to be suitable candidates for CAR T-cell therapy. The development of less toxic CAR T-cell products and facilitation of outpatient administration is expected to both lower costs and expand access to more community practice groups; however, there continues to be a significant need for noncellular therapy options for R/R DLBCL.

5.2. Selinexor

Selinexor blocks the transport of tumor suppressor, growth regulatory, and anti-inflammatory proteins, as well as oncoprotein mRNAs that induce tumor cell apoptosis [66]. A phase 2 study showing modest single-agent activity led to regulatory approval of selinexor for patients with R/R DLBCL who have received at least 2 lines of therapy [6]. Selinexor is recommended by the NCCN guidelines for patients only after at least 2 lines of systemic therapy, including patients who received cellular therapy [1]. The phase 2b, open-label, single-arm SADAL study evaluated selinexor 60 mg orally on days 1 and 3 of each week in 127 adult patients with R/R DLBCL or transformed DLBCL after receiving 2 to 5 lines of therapy [67]. Patients had either received or were not candidates for ASCT. Patients who had responded to their previous line of therapy had to be at least 60 days from their last treatment, and 14 weeks must have elapsed from the end of the last treatment for all other patients enrolled. Approximately one-fourth of patients had transformed DLBCL, 47% had GCB-like DLBCL, and 4% of patients had DHL/THL. Patients had received a median of 2 prior regimens, with 41% of patients receiving at least 3 prior regimens. Most patients (72%) were refractory to the most recent systemic treatment regimen for DLBCL. An ORR of 28% (95% CI, 20.7%–37.0%) was observed with 12% (95% CI, 6.8%–18.7%) of patients achieving a CR to selinexor. In a subgroup analysis, patients with the GCB subtype had an ORR of 34%, and patients with the non-GCB subtype had an ORR of 21%, though the confidence intervals for these response rates overlap. After a median of 14.7 months of follow-up, the median PFS was 2.6 months (95% CI, 1.9–4.0), and the median OS was 9.1 months (95% CI, 6.6–15.1). The most frequently observed grade 3 or 4 adverse events were hematologic, including thrombocytopenia (46%), neutropenia (26%), and anemia (22%); febrile neutropenia was observed in 3% of patients. Despite the use of antiemetic prophylaxis, nausea occurred in 58% of patients, and vomiting was reported in 29% of patients. Thrombopoietin receptor agonists and G-CSF were used in 17% and 24% of patients, respectively. The modest ORR coupled with twice-weekly oral administration with antiemetic premedication has limited the use of selinexor in DLBCL.

5.3. Antibody-drug conjugates

Antibody-drug conjugates were designed to enhance the toxicity of monoclonal antibodies by delivering a cytotoxic small molecule into the tumor [68]. ADCs comprise 3 discrete components: the antibody, the linker, and the cytotoxin [69]. The efficacy and toxicity of ADCs are largely based on the cytotoxin; however, the antibody and linker affect whether or not the cytotoxin reaches a target cell and is cleaved so it can exert cytotoxicity. Targeting an antigen with a higher expression on tumor cells relative to healthy tissues facilitates preferential delivery of a cytotoxin to the tumor cell [70]. The antibody must be capable of binding an antigen epitope and stimulating uptake into the tumor cell because the rate and extent of ADC internalization into the tumor cell affects the potential for toxicity to malignant and non-malignant cells. The development of chimeric and fully-humanized monoclonal antibodies led to the engineering of ADCs, which are less immunogenic and cause fewer infusion reactions. The stability of the linker connecting the antibody to the cytotoxin is a key determinate of ADC safety [70]. A stable linker prevents release of the cytotoxin into the systemic circulation. Most linkers mitigate toxicity by release of the cytotoxin within the intracellular environment due to acid-labile linkers or via cleavage of peptide linkers. Cell toxicity may result from the bystander effect, which occurs when target-negative cells near target cells are killed by the cytotoxin. The drug:antibody ratio and drug position affect the physical properties of the ADC, which influence aggregation, antigen binding, and clearance of the conjugate from the circulation.

Three ADCs are included in the NCCN guidelines for management of DLBCL: polatuzumab vedotin, brentuximab vedotin, and loncastuximab tesirine (Fig. 1) [1]. The mechanism of action is similar for all three ADCs. The ADC binds to an antigen on the surface of B cells: loncastuximab tesirine binds to CD19; brentuximab vedotin binds to CD30; polatuzumab vedotin binds to CD79b. The ADC is then internalized via endocytosis and degraded in lysosomes. This leads to release of the cytotoxin; tesirine releases PBD and vedotin releases MMAE. After the PBD dimer is released inside the cell, it creates covalent cross-links in the minor groove of the DNA. The irreversible alkylation results in disruption of cell replication and subsequent tumor cell apoptosis. MMAE may be released before internalization in the targeted cell and then enter the targeted cell or a nearby cell before disrupting tubulin and leading to apoptosis [71]. MMAE is diffused across the plasma membrane of the target antigen positive cells to reach target antigen negative tumor cells, exerting a bystander killing effect [71].

Resistance to ADCs may occur by the following: (1) downregulation of the targeted antigen; (2) impaired binding, trafficking, or internalization of the antibody; (3) degradation of the antibody; (4) reduced cleavage of the antibody from the cytotoxin; (5) resistance to auristatins; or (6) reduced drug retention within the cell (e.g., by upregulation of multidrug resistance transporters) [71].

5.3.1. Polatuzumab vedotin

Polatuzumab comprises a humanized IgG1 antibody targeting CD79b, a protease-cleavable maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl covalently bound to MMAE, an antimicrotubule cytotoxin [4]. A phase 1, open-label, dose-finding study determined polatuzumab 2.4 mg/kg administered every 21 days as the recommended phase 2 dose, with neutropenia as the dose-limiting toxicity [72]. The ORR in 27 patients with DLBCL at the recommended phase 2 dose was 56%, with 16% of patients achieving a CR. In this subgroup, a median PFS was 5.0 months (95% CI, 2.3–6.8), and the median DoR was 5.2 months (95% CI, 2.4–13.1). Subsequent studies of polatuzumab vedotin evaluated a lower dose of polatuzumab vedotin (1.8 mg/kg) and limited therapy to 6 to 8 cycles of therapy to mitigate the development of peripheral neuropathy. Despite a limited duration of response to monotherapy with polatuzumab vedotin, single-agent therapy may be considered prior to CAR-T leukapheresis as bendamustine may impact the success of T-cell collection.

5.3.2. Polatuzumab in combination with bendamustine and rituximab

Regulatory approval was granted to Pola-BR for R/R DLBCL after at least 2 prior therapies as a result of a randomized phase 2 trial in 80 transplant-ineligible patients showing a significant improvement in ORR, PFS, and OS, as compared with BR alone [73]. Patients with transformed lymphoma and grade 2 or higher peripheral neuropathy were excluded from the study. No patients with DHL/THL were included

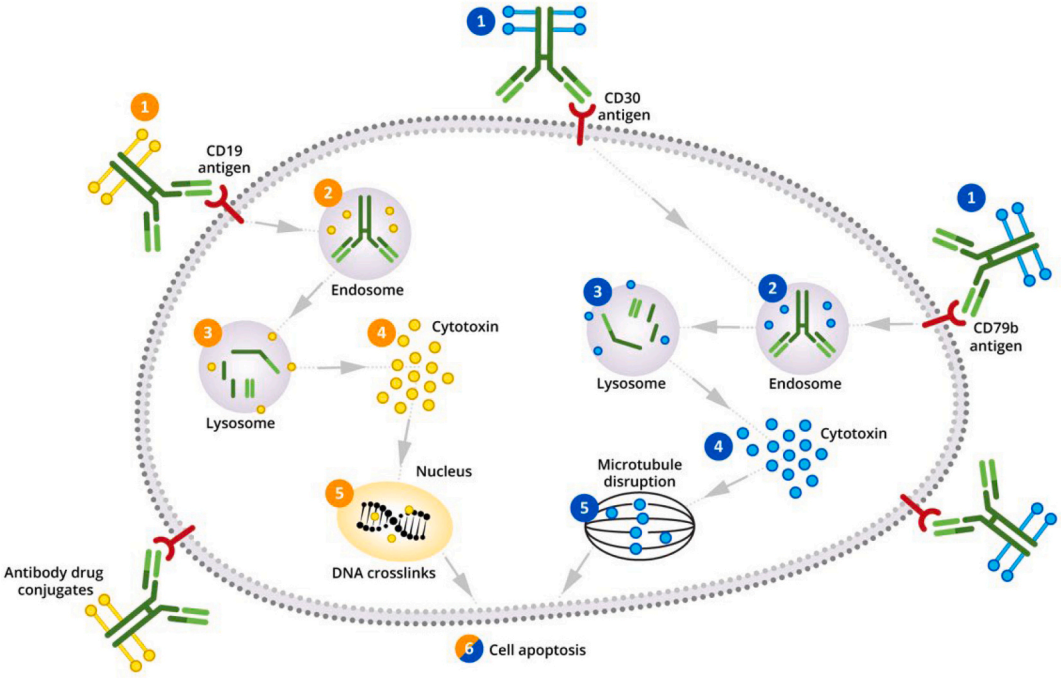

Fig. 1. Antibody drug conjugate mechanism of action in DLBCL .
1. ADC binds to antigen: loncastuximab tesirine binds to CD19 (left); brentuximab vedotin binds to CD30 (center); polatuzumab vedotin binds to CD79b (right). 2. Internalization via endocytosis. 3. Degradation of ADCs in lysosomes. 4. Release of cytotoxin: tesirine releases PBD (yellow circles); vedotin releases MMAE (blue circles). 5. Cytotoxin action: PBD dimer forms DNA cross-links and stalls DNA replication; MMAE leads to microtubule disruption. 6. Apoptosis of target cell.
ADC, antibody drug conjugate; DLBCL, diffuse large B-cell lymphoma; MMAE, monomethyl auristatin E; PBD, pyrrolobenzodiazepine.

in the study, and 47.5% had the ABC-like subtype DLBCL in both arms of the study. The median age was 67 years (range 33–86 years) in patients receiving Pola-BR and 71 years (range 30–84 years) in patients receiving BR. Patients had received a median of 2 prior lines of therapy, with fewer than 30% of patients receiving therapy in the second-line setting. Most patients were refractory to their last prior therapy (75% of Pola-BR and 80% of BR). One-fourth of patients receiving Pola-BR and 15% of BR patients had undergone prior ASCT. An ORR of 45% was observed in patients receiving Pola-BR compared with 17.5% of patients receiving BR, with a CR of 40.0% vs. 17.5%, respectively ($P = 0.026$). A median PFS of 9.5 months (95% CI, 6.2–13.9) and median OS of 12.4 months (95% CI, 9-not estimable) were observed with Pola-BR compared with 3.7 months (95% CI, 2.1–4.5) and 4.7 months (95% CI, 3.7–8.3), respectively, in patients receiving BR. Post hoc subgroup analysis of overall survival found that patients with the ABC subtype benefitted from Pola-BR relative to BR (HR 0.34, 95% CI 0.15–0.74), while the confidence interval for the GCB subtype suggests no benefit with the addition of polatuzumab vedotin (HR 0.56, 95% CI 0.24–1.29). Febrile neutropenia was observed in 10.3% of patients receiving Pola-BR and 12.8% of patients receiving BR; G-CSF was administered in 72% and 62% of patients, respectively. Peripheral neuropathy was observed in 44% of patients receiving Pola-BR; no patients developed grade 3 or higher peripheral neuropathy [74]. Common adverse events following Pola-BR included anemia (53.8%), neutropenia (53.8%), thrombocytopenia (48.7%), diarrhea (38.5%), fatigue (35.9%), pyrexia (33.3%), nausea (30.8%), and decreased appetite (25.6%) [74]. Approximately one-third of patients receiving Pola-BR discontinued therapy due to adverse events, with the most frequently observed being myelosuppression.

5.3.3. *Brentuximab vedotin*

Brentuximab vedotin is comprised of a chimeric anti–CD30 IgG1 antibody, the microtubule-disrupting agent MMAE, and a protease-cleavable linker that attaches the cytotoxin covalently to the antibody [70]. While it is not approved by the FDA for DLBCL, brentuximab vedotin is included in the NCCN guidelines as a regimen useful for patients with CD30+ expression DLBCL based on a phase 2, open-label study that demonstrated single-agent efficacy and manageable adverse effects [1,75]. Patients had received a median of three prior therapies, and 76% of patients were refractory to their most recent prior therapy. An ORR of 44% was observed in 48 patients with R/R DLBCL, with CD30 expression detectable by visual assessment of immunohistochemistry (IHC) on a biopsy; 17% of patients achieved a CR [75]. After a median follow-up of 4.6 months, the median PFS was 4 months (range, 0.6–29.5 months). No statistical correlation was observed between the response and CD30 expression as assessed by the visual central review, computer-assisted central review of IHC, or soluble CD30 assessed by bead-based sandwich fluoroimmunoassay.

5.3.4. *MMAE cytotoxin-related toxicities*

Polatuzumab and brentuximab are conjugated to the vedotin molecule to deliver MMAE, a tubulin polymerization inhibitor that leads to cell death [71]. Classic side effects of tubulin-targeted ADCs include peripheral neuropathy, neutropenia, thrombocytopenia, and anemia [69,76,77]. The bystander effect may contribute to off-target neurotoxicity with vedotin-based ADCs [71]. The most common adverse events observed with polatuzumab vedotin in the phase 1 study included neutropenia (40%), anemia (11%), and peripheral sensory neuropathy (9%) [72]. Frequently observed adverse effects following brentuximab vedotin administration attributed to MMAE include neutropenia (41%) and peripheral sensory neuropathy (29%) [75].

5.3.5. *Loncastuximab tesirine*

The human CD19 antigen is a type I membrane glycoprotein with expression preserved in various stages of B-cell development and differentiation and in the majority of B-cell malignancies, including DLBCL [,78,79]. CD19 is an ideal target for the development of ADCs due to rapid internalization kinetics and the absence of shedding into the

circulation [78]. Loncastuximab tesirine comprises a humanized IgG1 kappa monoclonal antibody to CD19, a protease-cleavable valine-alanine linker, and SG3199, a PBD cytotoxin [7]. Pyrrolobenzodiazepines are approximately 50 to 100 times more potent than conventional cytotoxins used in ADCs (e.g., MMAE in vedotin) [71]. Compared with other cytotoxin components, PBD dimers have a relatively short half-life, minimizing the bystander effect and systemic accumulation of free drugs, which could contribute to off-target toxicity [78]. In contrast to earlier generation PBD chemistry, PBD dimers are not a substrate for multidrug resistance proteins [71]. The PBD cross-links do not trigger DNA repair and are less visible to repair mechanisms; therefore, they can covertly persist in interrupting cell division, causing tumor cell death.

Loncastuximab tesirine received FDA approval and is recommended in the third-line setting in the NCCN guidelines based on the phase 2, single-arm LOTIS-2 study in 145 patients with R/R DLBCL [1,80]. In this study, treatment consisted of monotherapy with loncastuximab tesirine 0.15 mg/kg every 3 weeks for 2 cycles and then 0.075 mg/kg every 3 weeks for subsequent cycles for up to 1 year or until disease relapse or progression, unacceptable toxicity, or death [80]. Those few patients whose treating physicians requested therapy beyond 1 year were allowed to proceed. The median age was 66 years, with more than half of patients aged 65 years or older. Patients had received a median of 3 prior lines of therapy (range, 2–7 lines), 20% of patients had primary refractory DLBCL, and 17% and 9% of patients had received prior ASCT and CAR T-cell therapy, respectively. In contrast to studies of combination therapy with tafasitamab and lenalidomide or Pola-BR, the LOTIS-2 trial enrolled 11 (8%) patients with HGBCL with *MYC* and *BCL2* or *BCL6* rearrangements and 29 (20%) patients with DLBCL transformed from a low-grade lymphoma [80]. The cell-of-origin was unknown in approximately half of the patients, one-third had the GCB subtype, and 16% had the ABC subtype [80]. Patients with bulky disease $\geq$10 cm or clinically significant third space fluid accumulation were excluded from this study. The ORR to loncastuximab tesirine was 48.3%, with similar response rates observed in subgroup analyses of HGBCL (45.5%), transformed lymphoma (44.8%), and the ABC subtype (47.8%) [80]. The median time to first response was 41 days, and the median duration of response was 13.4 months [,80,81]. After a median follow-up of 7.8 months (range, 0.3–31.0 months), the median PFS was 4.9 months (95% CI, 2.89–8.31) and median OS was 9.5 months (95% CI, 6.93–11.47) [81]. Following loncastuximab tesirine, 4 patients received consolidation with an allogeneic SCT, and 5 patients received an ASCT. Fifteen patients subsequently received CAR T-cell therapy with an investigator-assessed response to CAR T-cell therapy of 47% and CR of 40% [80].

There is also a paucity of data on the use of sequential CD19-directed therapy. In the LOTIS-2 study, patients who had received previous CD19-directed therapy were required to have a biopsy showing CD19 expression. Thirteen patients received CAR T-cell therapy prior to loncastuximab tesirine; the ORR to loncastuximab tesirine was 46.2% in patients who had received CAR T-cell therapy prior to loncastuximab tesirine [80]. There is limited data on the effectiveness of treatment in patients progressing after CAR T-cell therapy, and the loss of CD19 expression may be a concern with the use of subsequent CD19-directed therapy. A study by Spiegel and colleagues reported a median time to progression of 91 days following axi-cel in 136 patients developing progressive disease [45]. The ORR to subsequent therapies ranged from 18% for chemotherapy to 46% for checkpoint inhibitor-based regimens with a median PFS range of 48 to 88 days. In the cohort of 61 patients that had biopsies assessed for CD19 expression, only 30% of samples were negative for CD19 expression [45]. Thapa et al. reported on 14 patients enrolled in the LOTIS-1 and LOTIS-2 studies with DLBCL relapsing or progressing a median of 4 months after treatment with loncastuximab tesirine who subsequently received CD19-directed CAR T-cell [82]. Six patients received additional lines of therapy between loncastuximab tesirine and CAR T-cell treatment. The ORR to CAR T-cell therapy administered after loncastuximab tesirine was 50%, with a complete response observed in 6 patients (43%). Ten (71%) patients underwent repeat biopsy between loncastuximab tesirine and CAR T-cell administration, and all were positive for CD19 expression based on immunohistochemical staining. The four patients with unknown CD19 expression status following loncastuximab tesirine achieved a CR to CAR T-cell therapy. A case report describes the response to CAR T-cell therapy in a single patient who received 6 cycles of tafasitamab and lenalidomide [83]. Additional data on the efficacy of sequential CD19 directed therapies is needed in R/R DLBCL.

5.3.6. Loncastuximab tesirine safety

At least 1 treatment-emergent adverse event (TEAE) was reported in almost all patients receiving loncastuximab tesirine [80]. The most frequently observed grade 3 or higher TEAEs were neutropenia (26%), thrombocytopenia (18%), and increased gamma-glutamyltransferase (GGT) (17%). Febrile neutropenia was reported in 3% of patients receiving loncastuximab tesirine, and growth factor support was permitted according to ASCO guidelines. Adverse events leading to discontinuation included increased GGT (10%), peripheral edema (3%), localized edema (2%), and pleural effusion (2%). Infusion-related reactions were observed in 7 (5%) patients in the LOTIS-2 trial during the first infusion and did not result in discontinuation of the infusion [80].

5.3.7. PBD cytotoxin-related toxicities

Toxicities considered likely to be related to the PBD cytotoxin included myelosuppression, edema and effusions, GGT elevation, and rash [77,80]. Hepatoxicity was minimal following loncastuximab tesirine, with grade 3 or higher elevations in alanine aminotransferase observed in 3% of patients, and grade 3 or higher elevations in aspartate aminotransferase, alkaline phosphatase, and bilirubin observed in 1% of patients [80]. Loncastuximab tesirine is associated with a moderate amount of myelosuppression with neutropenia in 57 (39%) patients, anemia in 38 (26%) patients, and thrombocytopenia in 48 (33%) patients [80]. In the LOTIS-2 study, edema or effusions occurred in 45 (31%) patients with grade 3 or higher events reported in 8 (5%) patients. Dexamethasone 4 mg orally twice daily for 3 days starting 1 day prior to administration was given in the LOTIS-2 study to reduce the incidence and severity of edema/effusions. Spironolactone was used to manage edema, weight gain greater than 1 kg from day 1 of cycle 1, and pleural effusions [80]. Skin rash and phototoxicity have been reported with both loncastuximab tesirine and rovalpituzumab tesirine and are attributed to the PBD dimer [77,80,84]. Patients should be advised to minimize or avoid exposure to direct natural or artificial sunlight, including exposure through glass windows, and to protect skin from exposure to sunlight by wearing sun-protective clothing and/or using sunscreen products [7].

6. Future considerations

Multiple clinical trials are underway to evaluate new combinations and novel therapies in R/R DLBCL. ADCs are being evaluated in combination therapy regimens in all lines of therapy. Phase 3 trials in progress evaluating ADCs include the LOTIS-5 trial comparing loncastuximab tesirine plus rituximab to rituximab, gemcitabine, and oxaliplatin (R-GemOx) for transplant-ineligible patients with DLBCL in the second-line setting; the POLARGO trial comparing polatuzumab vedotin plus R-GemOx to R-GemOx for transplant-ineligible patients with DLBCL in the second-line setting; and the ECHELON-3 trial comparing lenalidomide plus rituximab with brentuximab or placebo in patients with R/R DLBCL in the third-line setting who are ineligible for cellular therapy [85–87]. ADCs with novel targets currently in phase 1 clinical trials in patients with R/R DLBCL include STRO-001, an anti-CD74 monoclonal antibody conjugated to a maytansinoid cytotoxin; Trph-222, anti-CD22 monoclonal antibody conjugated to maytansine; and VLS-101, a monoclonal antibody targeting receptor tyrosine kinase-like orphan receptor 1 (ROR1) conjugated to MMAE (Table 4) [88–90]. Naratuximab emtansine, an ADC linking an anti-CD37 antibody to the cytotoxin DM1, has demonstrated efficacy in combination with

Table 4
Investigational ADCs and bispecific antibody therapies in DLBCL.

Reference	Study	Therapy	Target
Antibody-drug conjugate monotherapy in relapsed/refractory DLBCL			
Phase 1 [90]	NCT03833180	Zilovertamab vedotin (VLS-101)	ROR1
Phase 1 [89]	NCT03682796	Trph-222	CD22
Phase 1 [88]	NCT03424603	STRO-001	CD74
Antibody-drug conjugate combination therapy with rituximab in relapsed/refractory DLBCL			
Phase 2 [91]	NCT02564744	Naratuximab emtansine (Debio 1562) + rituximab	CD37
Bispecific antibody monotherapy in relapsed/refractory DLBCL			
EPCORE NHL-1 [94]	NCT03625037	Epcoritamab (GEN3013)	CD3 × CD20
NP30179	NCT03075696	Glofitamab (RO7082859)	CD3 × CD20
Phase 1 / 1b [93]	NCT02500407	Mosunetuzumab (BTCT4465A)	CD3 × CD20
Phase 1 [92]	NCT02290951	Odronextamab (REGN1979)	CD3 × CD20
Bispecific antibody combination therapy with antibody-drug conjugates in relapsed/refractory aggressive NHL			
NP39488 Phase 1b/2 [100]	NCT03533283	Glofitamab (RO7082859) + polatuzumab	CD3 × CD20
Phase 1b/2 [101]	NCT03671018	Mosunetuzumab (BTCT4465A) + polatuzumab	CD3 × CD20
Bispecific antibody combination therapy in first-line DLBCL			
EPCORE NHL-2 Phase 1/2 trial [102]	NCT04663347	Epcoritamab (GEN3013) + R-CHOP	CD3 × CD20
NP40126 Phase 1b/2 [103]	NCT03467373	Glofitamab (RO7082859) + R-CHOP	CD3 × CD20

ADCs, antibody-drug conjugates; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; ROR1, receptor tyrosine kinase-like orphan receptor 1.

rituximab in a phase 2 clinical trial in patients with R/R DLBCL (Table 4) [91].

Bispecific antibodies are another strategy to leverage the immune system in eradicating lymphoma cells by engaging one antigen on a malignant cell and another on T cells to bring immune effector cells in close proximity to malignant cells and trigger cell-mediated cytotoxicity of the malignant cell [52]. Several CD3 and CD20 bispecific antibodies are under investigation in DLBCL, including mosunetuzumab, epcoritamab, odronextamab, and glofitamab (Table 4) [92–95]. Similar to ADCs, bispecific antibodies are manufactured as off-the-shelf products, a significant advantage over CAR T-cell therapy because therapy can be initiated more quickly. Longer-term follow-up is needed to determine if bispecific antibodies provide durable remissions similar to CAR T-cell therapies. While the toxicity profile of bispecific antibodies appears improved over CAR T-cell therapy, the toxicity burden may be higher than with ADCs. FDA approval of bispecific therapies will add further complexity to treatment decisions for individual patients with R/R DLBCL.

7. Conclusion

The majority of patients diagnosed with DLBCL can be cured; however, a subset of patients will have multiple disease recurrences and ultimately succumb to the disease. Outcomes are poor for patients with progression after 3 or 4 lines of therapy, and fewer patients continue treatment with each subsequent line of therapy. Several new therapies have been approved by the FDA in a relatively short timeframe. Furthermore, several bispecific antibodies and novel ADCs are presently in development. Therefore, it is key to understand the nuances of novel therapies not only to determine which therapy is most appropriate for a given patient but also to guide future research into rationale combinations. Regardless of therapy, outcomes of R/R DLBCL differ substantially when categorized by the response to initial therapy, the timing of relapse, and prior cellular therapy; therefore, the design and interpretation of uncontrolled trials should account for this heterogeneity in patients with R/R DLBCL [16]. ADCs are a key component in the management of R/R DLBCL, and polatuzumab may receive guideline endorsement and FDA-approval for use in the first-line setting. Replacing vincristine with polatuzumab vedotin in R-CHOP improved PFS for patients with newly diagnosed DLBCL. Loncastuximab tesirine is a recent addition to the treatment landscape of R/R DLBCL that is effective in heavily pretreated patients with risk factors for poor outcomes, including HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements, primary refractory disease, and those who received prior cellular therapy. Multicenter group support is needed to lead comparative clinical trials to determine the optimal therapy sequences. Currently available and emerging therapies in DLBCL offer improvement in several outcome measures, with significant variability in efficacy, toxicity, and financial burden to the patient and healthcare system [96]. Assessments of cost, cost-effectiveness and patient-reported outcomes should play a role in treatment decisions for patients with DLBCL.

8. Practice points

- First-line therapy with Pola-R-CHP led to improvement in PFS compared with RCHOP in patients with intermediate-risk or high-risk DLBCL.
- Despite efficacy in the second-line or subsequent setting, relatively few patients receive CAR T-cell therapy, and off-the-shelf therapies are needed for patients with R/R DLBCL
- Loncastuximab tesirine is effective as a single agent in diverse and high-risk patient populations, including primary refractory and transformed DLBCL, patients who received prior cellular therapies, and those with HGBCL with *MYC* and *BCL2* or *BCL6* rearrangements.
- Manageable adverse events consistent with the PBD cytotoxin, including myelosuppression, edema and effusions, and cutaneous reactions, were observed with loncastuximab tesirine; implementation of dexamethasone before therapy is essential to decrease treatment-related toxicity.

Research agenda

- Define the optimal sequencing of therapies for R/R DLBCL.
- Further refine characteristics of the patient population who would benefit most from ADC therapy for DLBCL.
- Identify biomarkers of response and toxicity in DLBCL.

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Declaration of Competing Interest

JPA reports personal fees and research support from ADC Therapeutics outside of the submitted work and has an immediate family member who has served on advisory boards from Puma Biotechnology, Inovio Pharmaceuticals, Agios Pharmaceuticals, Forma Therapeutics, and Foundation Medicine.

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