The Emergence of Bispecific T-Cell Engagers in the Treatment of Follicular and Large B-Cell Lymphomas

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Abstract: The rapid emergence of CD20-targeting T-cell engagers in follicular lymphoma and large B-cell lymphoma has further expanded the treatment options for patients with relapsed or refractory disease. Herein, we review and discuss the standard-of-care products and indications for mosunetuzumab, epcoritamab, and glofitamab. We provide a detailed overview of the registrational clinical trials, as well as a review of ongoing trials and likely future indications. We also address how we incorporate T-cell engagers in our current treatment paradigm, with particular emphasis on their use with and as alternatives to chimeric antigen receptor T-cell therapy. We further discuss our management of immune effector cell–related toxicities.

Introduction

The monoclonal antibody rituximab earned US Food and Drug Administration (FDA) approval in 1997 for use in B-cell lymphoma (BCL). It has since been shown to improve survival when combined with conventional cytotoxic chemotherapy, representing a revolution in disease control based on harnessing the power of the body's own immune system.[1,2] Two decades after the approval of rituximab, in 2018, the FDA approved tisagenlecleucel (Kymriah, Novartis), a CD19-directed chimeric antigen receptor (CAR) T-cell therapy, for use in relapsed or refractory (R/R) large B-cell lymphoma (LBCL). The approval of this immune effector cell (IEC) therapy has been followed by the FDA approval of 4 additional CD19-targeting CAR T-cell therapy products.[3,4] Although CAR T-cell therapy has revolutionized the treatment landscape in R/R BCL, providing the first notable long-term survival benefit in decades, not everyone is a candidate. Possible toxicities include high-grade cytokine release syndrome (CRS), IEC-associated neurotoxicity syndrome (ICANS), prolonged cytopenias and infection, IEC-associated hemophagocytic lymphohistiocytosis–like syndrome, and secondary malignancies.[5-9] These toxicities are estimated to lead to a 5% to 10% risk of nonrelapse mortality in real-world studies.[10,11] With the FDA approval of mosunetuzumab (Lunsumio, Genentech) in late 2022, bispecific T-cell

Table 1. Follicular Lymphoma TCE Trials Leading to FDA Approval

	Mosunetuzumab*	Epcoritamab (EPCORE NHL-1)
Phase	2	2
Baseline characteristics		
Patients enrolled	90	128
Age, median (range), y	60 (53-67)	65 (55-72)
Female	35 (39%)	49 (38%)
Ethnicity: White	74 (82%)	Nrep
Ethnicity: Asian	8 (9%)	
Ethnicity: Black	4 (4%)	
ECOG: 0	53 (59%)	70 (55%)
ECOG: 1	37 (41%)	51 (40%)
ECOG: 2	0	7 (5%)
Stage I/II	21 (24%)	19 (15%)
Stage III/IV	69 (76%)	109 (85%)
Bulky disease (>6 cm)	31 (34%)	33 (26%)
Previous lines of therapy, median (range)	3 (2-4)	3 (2-4)
2 previous lines of therapy	34 (38%)	47 (37%)
3 previous lines of therapy	28 (31%)	41 (32%)
>3 previous lines of therapy	28 (31%)	40 (31%)
Previous alkylator therapy	90 (100%)	Nrep
Previous anti-CD20 therapy	90 (100%)	128 (100%)
Previous anthracycline therapy	74 (82%)	Nrep
Previous CAR T-cell therapy	3 (3%)	6 (5%)
Previous autoHCT	19 (21%)	Nrep
Refractory to last line of therapy	62 (69%)	88 (69%)
Refractory to anti-CD20 therapy	71 (79%)	101 (79%)
POD24	47 (52%)	67 (52%)
Therapeutic intervention		
Route of administration	IV	SC
Cycle duration	21 d, ≤7 cycles	28 d, indefinite
Dosing		
	C1D1 1 mg	C1D1 0.16 mg
	C1D8 2 mg	C1D8 0.8 mg
	C1D15, C2D1 60 mg	C1D15# 3 mg
	C3D1 onward 30 mg	C1D22, C2-3 weekly 48 mg
		C4-9 q2wk 48 mg
		C10+ monthly 48 mg

engagers (TCEs) have rapidly emerged as an additional immune-mediated therapy in BCL with a high degree of efficacy, decreased high-grade toxicities, and off-the-shelf availability, without the manufacturing delay of CAR T-cell therapy. No head-to-head comparisons of the TCEs and CAR T-cell therapy exist, and the most appropriate sequencing and use of these products remain to be seen. In this review, we seek to provide an overview of the currently available TCEs, their indications, the trials underway, our current institutional practices in their use, and how best to incorporate TCEs in the current treatment paradigm of small-molecule drugs, chemoimmunotherapies, and CAR

Table 1. *(Continued)* Follicular Lymphoma TCE Trials Leading to FDA Approval

	Mosunetuzumab*	Epcoritamab (EPCORE NHL-1)
Results		
Median follow-up, mo	18.3 (IQR 13.8-23.3)	17.4 (IQR 9.1-20.9)
First assessment	6 wk	6 wk
OR (rate)	72 (80%)	105 (82%)
CR (rate)	54 (60%)	80 (62.5%)
Time to response, mo	1.4 (95% CI, 1.2-2.9)	1.4 (IQR, 1.3-1.5)
Time to CR, mo	3 (95% CI, 1.4-5.7)	1.5 (IQR, 1.4-2.8)
DOR, median, mo	22.8 (9.7-NR)	Nrep
PFS, median, mo (95% CI)	17.9 (10.1-NR)	Nrep
OS, median	NR	NR
AEs/toxicities		
CRS grade 1-2/3-4	38 (42%)/2 (2%)	83 (65%)/2 (2%)
ICANS grade 1-2/3-4	3 (3%)/0	8 (6%)/0
Fever grade 1-2/3-4	25 (28%)/1 (1%)	29 (23%)/3 (2%)
Neutropenia grade 1-2/3-4	2 (2%)/24 (26%)	4 (3%)/32 (26%)
Anemia grade 1-2/3-4	5 (6%)/7 (8%)	11 (9%)/8 (6%)
Thrombocytopenia grade 1-2/3-4	5 (6%)/4 (4%)	11 (9%)/5 (4%)
Any grade 5 event	0	6 (5%)

*Independent review committee assessment reported.
#In the optimization cohort, the C1D15 dose of 3 mg was given to reduce the incidence of CRS and ICANS and allow all-outpatient administration.

AE, adverse event; autoHCT; autologous hematopoietic cell transplant; C1D1, cycle 1 day 1; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; d, days; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group score; FDA, US Food and Drug Administration; ICANS, immune effector cell–associated neurotoxicity syndrome; IQR, interquartile range; IV, intravenous; mo, months; NR, not reached; Nrep, not reported; OR, objective response; OS, overall survival; PFS, progression-free survival; POD24, progression of disease within 24 months; q2wk; every 2 weeks; SC, subcutaneous; TCE, T-cell engager; wk, weeks; y, years.

T-cell therapies. Because of the shortcomings of cross-trial comparisons, we prefer to review the similarities and differences among trial findings.

Mechanism of Action of TCEs

The mechanism of action of TCEs involves harnessing the killing power of recipient T lymphocytes to engage lymphoma cells directly. Although each TCE construct has a slightly different approach, in the realm of BCL-targeted therapies, one end of the immunoglobulin G–based TCE binds CD20 on the lymphoma while the other binds CD3 on the T-lymphocyte–T-cell receptor (TCR) complex. This strategy does not require TCR-major histocompatibility complex I engagement for T-lymphocyte activation. T-lymphocyte activation occurs upon the interaction of CD3 on the T lymphocyte and CD20 on the target cell, leading to the release of cytotoxic substances like perforin and granzyme B to induce apoptosis of the target cell.[12] Additionally, inflammatory cytokines such as interleukin 1 (IL-1), IL-6, IL-10, interferon-γ, and tumor necrosis factor are secreted, propagating the T-lymphocyte–led immune response and leading to the potential toxicities of CRS and ICANS.[13] Although all 3 currently FDA-approved TCE products for B-cell lymphoma (mosunetuzumab, epcoritamab [Epkinly, Genmab/AbbVie], and glofitamab [Columvi, Genentech]) target CD20, they target different epitopes on the CD20 antigen. Mosunetuzumab is identical to rituximab, epcoritamab is identical to ofatumumab (Arzerra, Novartis), and glofitamab is identical to obinutuzumab (Gazyva, Genentech).[14] Uniquely, glofitamab has a 2:1 CD20:CD3 molecular format, with 2 CD20-binding sites per molecule.[15]

TCEs in R/R Follicular Lymphoma

The TCEs mosunetuzumab and epcoritamab are currently approved for grades 1-3a R/R follicular lymphoma (FL) after 2 lines of therapy (Table 1). The registrational clinical trials for both products were single-arm phase 2

trials, although the mosunetuzumab trial did an analysis comparison with the phosphoinositide 3-kinase inhibitors idelalisib (Zydelig, Gilead) and copanlisib as historical comparators.[16,17] The population in the mosunetuzumab trial was younger than that in the epcoritamab trial (median age, 60 vs 65 years), and the proportions of female participants were similar. The population was predominately White (82%) in the mosunetuzumab trial and not reported in the epcoritamab trial. Similar numbers of patients had an Eastern Cooperative Oncology Group (ECOG) score of 0 to 1 in the 2 trials. No patients had an ECOG of 2 in the mosunetuzumab trial, and 5% of patients had an ECOG of 2 in the epcoritamab trial. Nearly 80% of patients had high stage III/IV disease in both trials (76% vs 85%). Both trials had a heavily pretreated population, with 2 or more previous lines of therapy that included an anti-CD20 monoclonal antibody and an alkylating agent (an alkylating agent or lenalidomide in the epcoritamab study). Approximately 60% of patients in both trials had 3 or more lines of therapy (62% vs 63%). Bulky disease, defined as greater than 6 cm, was more common in the mosunetuzumab trial than in the epcoritamab trial (34% vs 26%). Only a very small number of patients had previous CAR T-cell therapy (3% vs 5%). In both trials, most patients had disease refractory to anti-CD20 monoclonal antibodies (69%) and to the last line of therapy (79%), and most were classified as having had progression of disease within 24 months (POD24; 52%).

The route of administration was intravenous (IV) for mosunetuzumab and subcutaneous for epcoritamab. Mosunetuzumab could be administered on an all-outpatient basis, with weekly step-up infusions of 1, 2, and 60 mg during cycle 1 followed by a 60-mg infusion on cycle 2 day 1 and then 30 mg every 3 weeks from cycle 3 day 1 onward for up to 17 cycles if the patient was responding and the drug was tolerated. Corticosteroid premedication with 20 mg of dexamethasone or the equivalent was given intravenously 1 hour before the infusion in cycles 1 and 2 and was optional thereafter. In the FL optimization cohort, epcoritamab was administered on an all-outpatient basis. The drug was dosed weekly in cycle 1 with step-up dosing of 0.16, 0.8, 3, and 48 mg. The dosing was 48 mg weekly in cycles 2 to 3, followed by 48 mg every 2 weeks in cycles 4 through 9 and then monthly from cycle 10 onward. Corticosteroid premedication in the optimization cohort was 15 mg of dexamethasone given 30 minutes to 2 hours before infusion, followed by 3 consecutive days of treatment for cycle 1.

The median follow-up was approximately 1.5 years in both trials (18.3 vs 17.4 months). At the first assessment, which occurred at 6 weeks, the objective response rate (ORR) and the complete response (CR) rate were approximately 80% and 60% in the 2 trials. The median time to achieve a CR was 3 months in the mosunetuzumab trial and 1.5 months in the epcoritamab trial, although some patients in both trials later achieved a CR. The median duration of response (DOR) was 22.8 months for mosunetuzumab and not reported for epcoritamab. The median progression-free survival (PFS) was 17.9 months for mosunetuzumab, and the 18-month PFS rate was 49% for epcoritamab. Median overall survival (OS) was not reached at the time of publication in either study. The 3-year results of this trial were presented at the 2023 American Society of Hematology (ASH) Annual Meeting. At a median follow-up of 37.4 months (2-48), the median DOR was 36 months (95% CI, 20.7-not reached) and the median duration of CR (DOCR) was not reached. The estimated 30-month DOCR rate was 72%, showing a durable long-term response.[18]

CRS and ICANS were almost exclusively low-grade in both trials. The incidence of low-grade (grades 1 and 2) CRS was lower for mosunetuzumab than for epcoritamab (42% vs 65%), with only 2% of patients having high-grade (grades 3 and 4) CRS in both trials. ICANS was low-grade only in both trials, but the rate was slightly lower in the mosunetuzumab trial (3% vs 6%). High-grade (grade 3 or 4) neutropenia occurred in about one-quarter of the patients in both trials. In the epcoritamab trial, 6 grade 5 events (5%) were reported that were due to COVID-19 infection.

TCEs in R/R Large B-Cell Lymphoma

The trial design and population of patients with R/R after more than 2 lines of therapy were similar for both glofitamab and epcoritamab, although a number of differences are worth highlighting (Table 2).[19,20] The glofitamab trial was phase 2, whereas the epcoritamab trial was phase 1/2.

The number of patients (154 vs 157) and the median age (66 vs 64 years) were similar in the 2 studies. In both studies, more men than women were enrolled, and ethnicity was not reported in either trial. The number of patients with an ECOG of 0 was nearly 50% in both trials. However, of note, the inclusion criteria were ECOG 0-1 for glofitamab and 0-2 for epcoritamab, although only 5 patients (3%) had an ECOG of 2. Nearly 90% of patients had diffuse LBCL (this included de novo and transformed histologies) in both trials. In the epcoritamab trial, 5 patients (3%) had grade 3B FL. Similar minorities (<10%) of patients with high-grade BCL, not otherwise specified, and primary mediastinal BCL were included in the 2 trials. Patients with active central nervous system (CNS) disease involvement or a history of previous CNS disease involvement were excluded in both trials. Most

patients (75%) in both trials had advanced stage III/IV disease and were heavily pretreated, with a median of 3 lines of previous therapy, previous anthracycline therapy, previous CAR T-cell therapy (33% vs 39%), and previous autologous hematopoietic cell transplant (autoHCT; 18% vs 20%), and more than 80% had disease that was refractory to the last line of therapy in both trials.

The route of administration is IV for glofitamab and subcutaneous for epcoritamab. The early use of corticosteroid premedication is recommended for both treatments to reduce the risk of CRS and ICANS. For glofitamab, 20 mg of IV dexamethasone (or an equivalent corticosteroid) is given at least 1 hour before administration for cycles 1 to 3. If the patient experiences any-grade CRS, it is recommended to continue this corticosteroid dose until CRS no longer occurs with treatment. For epcoritamab, 15 mg of IV dexamethasone (or an equivalent corticosteroid) is given 30 to 120 minutes before administration and for 3 consecutive days in the initial weekly dosing. The corticosteroid is continued in cycle 2 and beyond only if the patient experiences grade 2 or higher CRS.

Glofitamab treatment should be permanently discontinued if recurrent grade 3 or any grade 4 CRS occurs. Acetaminophen and an antihistamine are recommended as pretreatment for all cycles. Epcoritamab treatment should be permanently discontinued if a patient experiences grade 4 or higher CRS. Prophylaxis for *Pneumocystis jirovecii* pneumonia and herpesvirus infection is recommended during treatment with either product. Given that 1 case of cytomegalovirus (CMV) chorioretinitis was reported in the glofitamab phase 1 trial, the FDA label includes consideration of prophylaxis.[15] In our clinical practice, we check an initial serum CMV level before treatment and then monthly thereafter while the patient is on treatment.

Glofitamab is scheduled on 21-day cycles to continue for a total of up to 12 cycles. An initial dose of obinutuzumab is followed by a cycle 1 day 8 step-up dose of 2.5 mg of glofitamab. This cycle 1 day 8 dose is typically given in the hospital to monitor for CRS and ICANS. It is followed a week later by a 10-mg dose for cycle 1 day 15, and then the full dose of 30 mg is given every 3 weeks from cycle 2 onward. Epcoritamab is scheduled to be administered on 28-day cycles to be continued indefinitely if the patient is responding and the drug is tolerated. The first dose of 0.16 mg is followed a week later by 0.8 mg and then a full dose of 48 mg on cycle 1 day 15, which is typically administered on an inpatient basis for monitoring. The next week, another 48-mg dose is given; this is continued weekly for cycles 2 and 3, and then every 2 weeks for cycles 4 through 9, and then monthly for cycle 10 and beyond. In both studies, initial staging was done at 6 weeks. For glofitamab, restaging studies were done after cycles 2, 5, and 8 and at the end of treatment—cycle 12—followed by restaging every 6 months until progression. For epcoritamab, restaging studies with imaging and measurable residual disease (MRD) testing were done at weeks 6, 12, 18, 24, 36, and 48 and every 24 weeks thereafter.

Both trials had a median follow-up time of less than 1 year (9 vs 11 months). The ORR by an independent review committee was slightly higher for epcoritamab (52% vs 63%), with identical CR rates (39%). The median time to CR was 1.5 months for glofitamab and 2.7 months for epcoritamab, although late responses at 11 months were seen in both trials. The median DOR was more than 1 year in both studies (18.4 vs 12 months), although it was 6 months longer in the glofitamab trial. The PFS in the 2 studies was 4.9 months (95% CI, 3.4-8.1) for glofitamab vs 4.4 months (95% CI, 3.7-7.9) for epcoritamab, and the OS in the 2 studies was 11.5 months (95% CI, 7.9-15.7) for glofitamab vs not reached for epcoratimab.

The toxicity profile was notable for predominately low-grade CRS in both studies, with slightly higher rates of low-/high-grade CRS for glofitamab (62%/4% vs 47%/2.5%) and a low incidence of any-grade ICANS in both studies (<6%). Interestingly, toxicity was observed more commonly at cycle 1 day 8 with glofitamab and at cycle 1 day 15 with epcoritamab. COVID-19 infection was seen in both studies (3% vs 6.4%), with an any-grade neutropenia rate of greater than 20% in both studies and a higher incidence of high-grade neutropenia with glofitamab. The rates of high-grade (grade 3 or 4) anemia and thrombocytopenia were 10% or less in both studies. The rates of grade 5 events were comparable in the 2 studies (5% vs 6%); most cases were due to infection.

Future Directions of TCEs in B-Cell Lymphoma

At the time of this writing, numerous studies are underway that use TCEs alone or in combination with other agents, with preliminary results. We highlight some trials of particular interest in the treatment of FL and LBCL. We caution that at the time of writing, many of these studies have been presented only in abstract form, with the final full-length manuscripts yet to be published.

Follicular Lymphoma

Many trials are underway for FL grades 1 through 3a. The EPCORE NHL-2 study has 5 arms: (1) epcoritamab plus bendamustine/rituximab (BR) and (2) epcoritamab plus lenalidomide/rituximab (R^2) as first-line treatment; (3) maintenance epcoritamab after response to standard-of-care (SOC) therapy; (4) epcoritamab plus R^2

Table 2. Large B-Cell Lymphoma TCE Trials Leading to FDA Approval

	Glofitamab*	Epcoritamab (EPCORE NHL-1)
Phase	2	1/2
Baseline characteristics		
Patients enrolled	154	157
Age, median (range), y	66 (21-90)	64 (20-83)
Female	54 (35%)	63 (40%)
Ethnicity	Nrep	Nrep
ECOG: 0	69 (45%)	74 (47%)
Diffuse LBCL High-grade BCL, NOS Primary mediastinal BCL FL, grade 3B	137 (89%) 11 (7%) 6 (4%) Not enrolled	139 (89%) 9 (6%) 4 (2%) 5 (3%)
Stage I/II	35 (22%)	39 (25%)
Stage III/IV	116 (75%)	118 (75%)
Bulky disease >6 cm Bulky disease >10 cm	64 (42%) 18 (12%)	Nrep Nrep
Previous lines of therapy, median (range)	3 (2-7)	3 (2-11)
2 previous lines of therapy	62 (40%)	46 (29%)
≥3 previous lines of therapy	92 (60%)	111 (71%)
Previous anti-CD20 therapy	154 (100%)	Nrep
Previous anthracycline therapy	149 (97%)	154 (98%)
Previous CAR T-cell therapy	51 (33%)	61 (39%)
Previous autoHCT	28 (18%)	31 (20%)
Refractory to last line of therapy	132 (86%)	130 (83%)
Refractory to anti-CD20 therapy	128 (83%)	Nrep
Refractory to CAR T-cell therapy	46 (30%)	46 (29%)+
Therapeutic intervention		
Route of administration	IV	SC
Cycle duration	21 d, up to 12 cycles	28 d, indefinite
Dosing		
	C1D1 obinutuzumab 1000 mg	C1D1 0.16 mg
	C1D8 2.5 mg	C1D8 0.8 mg
	C1D15 10 mg	C1D15,D22 48 mg
	C2D1 onward 30 mg	C2-3 weekly 48 mg
		C4-9 q2wk 48 mg
		C10+ monthly 48 mg

for R/R disease; and (5) epcoritamab plus lenalidomide for progression of disease within 24 months (POD24).[21] Epcoritamab plus R^2 as first-line treatment demonstrated a remarkably high ORR and CR rate (95% and 85%, respectively), with a 66% incidence of mostly low-grade CRS and no ICANS.[22] This combination in the R/R setting, including POD24, demonstrated similar efficacy (97% ORR, 86% CR rate), with a lower reported CRS rate (48%) and a low incidence of ICANS (2%).[23] Maintenance epcoritamab following initial SOC therapy was also demonstrated to have similar safety, with a number of partial responses converting to CR on maintenance. Another CD2-CD20 TCE, odronextamab (Odronextamab, Regeneron), has been studied in R/R FL in the phase 1 ELM-1 study, with an ORR and a CR rate of 91% and 72%, respectively, and mostly low-grade CRS

Table 2. *(Continued)* Large B-Cell Lymphoma TCE Trials Leading to FDA Approval

	Mosunetuzumab*	Epcoritamab (EPCORE NHL-1)
Results		
Median follow-up, mo	9 (range, 0.1-16)	11
First assessment	6 wk	6 wk
OR (rate)	80 (52%)	99 (63%)
CR (rate)	61 (39%)	61 (39%)
Time to response, median (range), mo	Nrep	1.4 (1-8.4)
Time to CR, median (range), mo	1.5 (1-11)	2.7 (1.2-11.1)
DOR, median (95% CI), mo	18.4 (13.7-NR)	12 (6.6-NR)
PFS, median, (95% CI), mo	4.9 (3.4-8.1)	4.4 (3-7.9)
OS, median, (95% CI), mo	11.5 (7.9-15.7)	NR (11.3-NR)
AEs/toxicities		
CRS grade 1-2/3-4^	95 (62%)/6 (4%)	74 (47%)/4 (2.5%)
ICANS grade 1-2/3-4$	8 (5%)/4 (3%)	9 (6%)/1 (0.6%)
COVID-19 infection	4 (3%)	10 (6.4%)
Neutropenia grade 1-2/3-4	Nrep/41 (27%)	11 (7%)/23 (14.6%)
Anemia grade 1-2/3-4	Nrep/10 (6%)	12 (8%)/16 (10%)
Thrombocytopenia grade 1-2/3-4	Nrep/12 (8%)	12 (8%)/9 (6%)
Any grade 5 event	8 (5%)	9 (6%)

*Independent review committee assessment reported.
+Progressed within 6 months of CAR T-cell therapy.
^CRS grading per Lee criteria.
$ICANS grading by CTCAE v4 for glofitamab and Lee criteria for epcoritamab.

AE, adverse event; autoHCT; autologous hematopoietic cell transplant; BCL, B-cell lymphoma; C1D1, cycle 1 day 1; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; d, days; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group score; FDA, US Food and Drug Administration; FL, follicular lymphoma; ICANS, immune effector cell–associated neurotoxicity syndrome; IV, intravenous; LBCL, large B-cell lymphoma; NOS, not otherwise specified; mo, months; NR, not reached; Nrep, not reported; OR, objective response; OS, overall survival; PFS, progression-free survival; q2wk, every 2 weeks; SC, subcutaneous; TCE, T-cell engager; wk, weeks; y, years.

(61%) and ICANS (12%).[24] Of note, odronextamab has a more complex initial dosing schedule during cycle 1, with dosing on days 1, 2, 8, 9, 15, and 16.

Large B-Cell Lymphoma

A variety of combination therapies have been explored in LBCL as both first and later lines of therapy. Glofitamab plus rituximab, polatuzumab, cyclophosphamide, daunorubicin, and prednisone (R-pola-CHP) as frontline treatment in LBCL demonstrated an ORR of 100%, a CR rate of 77%, CRS in 83% of patients (mostly low-grade), and no ICANS.[25] The EPCORE NHL-2 study included 5 arms in LBCL: (1) frontline epcoritamab plus rituximab, cyclophosphamide, daunorubicin, vincristine, and prednisone (R-CHOP) and (2) epcoritamab plus R-mini-CHOP in those ineligible for full-dose anthracycline; (3) epcoritamab plus rituximab, cytarabine, dexamethasone, oxaliplatin, and carboplatin (R-DHAX/C) for transplant-eligible R/R LBCL; (4) epcoritamab plus rituximab, gemcitabine, and oxaliplatin (R-GemOx) for transplant-ineligible R/R LBCL; and (5) epcoritamab plus rituximab, ifosfamide, and etoposide (R-ICE) for transplant-eligible R/R LBCL. The EPCORE NHL-2 study also included an arm of epcoritamab plus R-CHOP as first-line therapy, with an ORR of 100% and a CR rate of 76%. CRS occurred in 59% of patients and was mostly low-grade. There was 1 case of grade 2 ICANS.[26] Similarly, in the elderly (>75 years) or those older than 65 years with 1 or more comorbidities, epcoritamab plus R-mini-CHOP demonstrated an ORR of 100% and a CR rate of 85%. The incidence of CRS was 43%, mostly low-grade, and no cases of ICANS were noted.[27] The EPCORE NHL-3 study demonstrated reasonable efficacy of epcoritamab as a single agent in R/R

LBCL, with an ORR of 56% and a CR rate of 44%. CRS occurred in 83% of patients and was mostly low-grade; 1 case of ICANS was reported, which quickly resolved.[28] Arm 4 of EPCORE NHL-3 also included epcoritamab plus R-DHAX/C for transplant-eligible R/R LBCL, with an ORR of 76% and a CR rate of 69%. Low-grade CRS occurred in 45% of patients, and 1 case of grade 2 ICANS.[29] Results from the epcoritamab-plus-GemOx arm of the EPCORE NHL-2 trial demonstrated an ORR and a CR rate of 91% and 59%, respectively, with mostly low-grade CRS and little ICANS.[30] The STARGLO3 study of glofitamab plus GemOx demonstrated a survival benefit over GemOx alone in LBCL that relapsed after 1 or more lines of therapy in transplant-ineligible patients (25.5 vs 12.9 months, respectively) and an improved CR rate (58.5% vs 25.3%, respectively), with CRS in 44.2% of patients (mostly low-grade) and minimal ICANS.[31] The ELM-2 study was a phase 2 study of single-agent odronextamab in R/R LBCL, with an ORR and a CR rate of 56% and 31%, respectively. The incidence of mostly low-grade CRS was 55%, with no ICANS.[32] To date, the FDA has declined to approve odronextamab in LBCL and FL and has issued 2 complete response letters related to enrollment status.[33]

Discussion

The last decade has seen one of the most significant leaps forward in the treatment of FL and LBCL with the approval and widespread adoption of CD19-directed CAR T-cell therapy and, more recently, CD20-directed TCE therapies. These therapies have improved efficacy and outcomes in patients with chemorefractory disease in comparison with the historical SOC outcomes of high-dose chemotherapy and autoHCT.[34,35] Herein, we have discussed the currently FDA-approved indications for the SOC treatment of R/R FL with mosunetuzumab and epcoritamab and the treatment of R/R LBCL with glofitamab and epcoritamab. Quite a bit of heterogeneity exists regarding prophylactic corticosteroid use and imaging timing with TCEs. It is our clinical practice to obtain initial restaging imaging at approximately 6 weeks with all TCE products and then at the end of treatment with mosunetuzumab and glofitamab and at approximately cycle 10 with epcoritamab in those whose initial imaging is consistent with a good response (Deauville score of 1-3 by the Lugano classification criteria). If refractory or progressive disease is a clinical concern, we image with greater frequency. MRD testing was used in most TCE studies and was prognostic. However, we do not typically use MRD testing in our practice outside the clinical trial setting at this time.

The TCE therapies in the R/R setting provide an additional option in an ever-growing space. The exact sequencing of TCE and CAR T-cell therapy remains unknown, and although the response rates of TCE therapy may be comparable with those of CAR T-cell therapy, we caution against using them interchangeably, given the differences in patient populations and trial design and the limited follow-up time with TCE therapy compared with CAR T-cell therapy. Until further maturation of trial and long-term real-world data, and with an understanding that a head-to-head trial is unlikely, we take an individualized, patient-by-patient approach to determining the most appropriate course of therapy. In R/R FL, CAR T-cell therapy appears to have less of a response advantage over TCEs than in LBCL. With that said, in young patients with few comorbidities and those preferring a "one and done" approach, we prefer CAR T-cell therapy. In patients who are older or are less able to tolerate high-grade CRS or ICANS, we prefer TCE therapy. In those who have R/R FL with suspicion for large cell transformation that is unconfirmed by biopsy, we prefer epcoritamab over mosunetuzumab. When patients who have R/R FL are frail, we tend to prefer mosunetuzumab, given the likely lower incidence of CRS. Our preference in LBCL is CAR T-cell therapy when possible (construct-dependent), with TCE therapy for those of advanced age or with comorbidity. For high-grade BCL in particular, our preference is CAR T-cell therapy over TCE, given than none of 11 of patients with high-grade histology achieved a CR in the glofitamab trial. This treatment practice is in line with a recently published meta-analysis of 724 CAR T-cell therapy patients from 10 studies and 605 TCE patients from 6 studies, which demonstrated increased efficacy in terms of CR rate and 1-year PFS, although toxicity was increased with CAR T-cell therapy in the third-line or later treatment of R/R LBCL.[36] In regard to sequencing, the use of TCEs before CAR T-cell therapy (as well as the inverse) outside clinical trials does not appear to affect CAR T-cell efficacy negatively and can be used in CAR T-cell therapy–eligible patients who have reservations about pursuing CAR T-cell therapy as the next line of treatment.[37] In instances of CAR T-cell therapy failure/relapse—particularly early failure in which TCE and CAR-T cell synergy may occur whereby the CD3 moiety may in theory engage CD19 on the CAR, improving its killing potential—we employ a TCE.[38] Furthermore, in the previously discussed clinical trials, approximately one-third of patients enrolled had had prior CAR T-cell therapy and achieved TCE response rates similar to those in the CAR T-cell–naive population. We do not typically use CD20 TCEs as bridging therapy before CAR T-cell therapy, given the length of time needed to achieve a full dose and the ever-decreasing manufacture time of autologous CAR T-cell therapy products. However, TCE bridging before CAR T-cell therapy has been

described with success in multiple myeloma.[39] Recently, in instances in which a rapid response is needed, and in patients who can tolerate increased toxicity, we have done a rapid ramp-up with glofitamab or epcoritamab, achieving a full dose within 7 and 5 days, respectively. With an accelerated step-up timetable, the use of TCEs as bridging therapy before CAR T-cell therapy may be possible, but we again stress that this is not our typical practice at this time. We believe that epcoritamab and glofitamab have comparable efficacy and toxicity, and we discuss the benefits and potential shortcomings of each with our patients. For those preferring a subcutaneous or indefinite treatment, we recommend epcoritamab. For those wanting less-frequent therapy with a fixed duration, we recommend glofitamab. In patients with CNS disease that is chemorefractory and for whom CAR T-cell therapy has not been an option, we have used TCEs, although there are only limited but promising data demonstrating TCE penetration through the blood-brain barrier and T-cell activation in the CNS.[40] Additionally, although those with low CD20 expression have responded to TCEs, we use the TCEs with extreme caution in patients who are negative for CD20 by immunohistochemistry or flow cytometry. In the glofitamab R/R LBCL trial, 3 patients with initially CD20-negative disease all had progressive disease as their best response and died during follow-up.[41] In instances of a loss of response, we repeat biopsy to confirm that CD20 expression remains because antigen escape has been demonstrated to be a potential mechanism of relapse in CD20-directed TCEs, akin to CD19 CAR T-cell therapy as described previously.[42]

As with CAR T-cell therapy, in which nonrelapse mortality is reported to be from 5% to 10% and due mostly to infection, infection with TCEs remains the largest concern for morbidity and mortality outside the initial toxicities of CRS/ICANS and disease progression. This is evidenced by the number of grade 5 infections, driven largely by the COVID-19 pandemic, with 5% of patients dying in the FL epcoritamab cohort. To reduce this risk, we frequently administer granulocyte colony–stimulating factor for an absolute neutrophil count of less than 1000/μL or intravenous immunoglobulin for immunoglobulin G levels below 200 mg/dL (or <400 mg/dL if the patient has had recurrent infections); provide prophylaxis for herpes simplex virus and *P. jirovecii* pneumonia during treatment; and monitor for CMV infection via CMV serum polymerase chain reaction before cycle 1 and thereafter if we suspect reactivation or infection.

Although much remains to be elucidated in terms of the sequencing and use of TCEs, they have rapidly emerged as a practice-changing addition to the treatment of R/R FL and LBCL. As we advance into the future, we look forward with great excitement to optimizing the use of combined therapies with TCEs in both the front-line and R/R settings and the potential for TCEs to become a more readily adoptable modality in the community vis-à-vis CAR T-cell therapy.

Disclosures

Dr Lutfi has had a past financial relationship with ADC Therapeutics. Dr Ahmed has financial relationships with Kite/Gilead, Legend Biotech, and Bristol Myers Squibb. Dr Hoffmann has financial relationships with ADC Therapeutics, Janssen, Pharmacyclics, BeiGene, Novartis, Astra Zeneca, AbbVie, Kite, TG Therapeutics, Genentech, and Bristol Myers Squibb. Dr Tun has no financial disclosures. Dr McGuirk has financial relationships with Envision Pharma Group, Kite, SciMentum, AlloVir, Bristol Myers Squibb, Novartis, CRISPR Therapeutics, Nektar, Caribou Biosciences, Sana Biotechnology, Legend Biotech, Cargo Therapeutics, and Autolus Therapeutics.

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