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CD20×CD3 Bispecific Antibodies in Relapsed/Refractory B-Cell Lymphomas: Recent Phase III Evidence Durability, and Safety

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ABSTRACT

CD20×CD3 bispecific antibodies (bsAbs) epcoritamab, glofitamab, mosunetuzumab, and odronextamab have become important treatment options in selected relapsed/refractory (R/R) B-cell lymphoma settings. This narrative review synthesizes trial evidence through August 2026, emphasizing randomized phase 3 data. In R/R diffuse large B-cell lymphoma (DLBCL), glofitamab plus chemotherapy improved overall survival versus chemoimmunotherapy in the randomized STARGLO trial (3-year median OS 25.5 vs 12.5 months; hazard ratio [HR] 0.60); epcoritamab improved progression-free survival but not overall survival versus chemoimmunotherapy in the EPCORE DLBCL-1 topline results. In R/R follicular lymphoma (FL), adding epcoritamab to lenalidomide-rituximab (R2) improved progression-free survival (HR 0.21) and response rates versus R2 alone in the randomized EPCORE FL-1 trial. Single-arm phase 1/2 data show substantial but less certain activity for these agents and for odronextamab in DLBCL and FL. Cytokine release syndrome is the dominant early toxicity, generally low-grade with step-up dosing; immune effector cell-associated neurotoxicity syndrome (ICANS) is less frequent but has been associated with fatal events in the epcoritamab DLBCL registrational population. Infection risk, including fatal infection, is clinically important with prolonged exposure. This is a narrative, non-systematic review; single-arm and uncontrolled results should not be read as directly comparable across agents.

الأجسام المضادة ثنائية النوعية CD20×CD3 في سرطان الدم اللمفاوي للخلايا البائية الناكس أو المقاوم للعلاج: أدلة حديثة من التجارب السريرية للمرحلة الثالثة، ومدة الاستجابة، والسلامة

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الكلمات المفتاحية:
CD20×CD3
جسم مضاد ثنائي النوعية
خلايا تي معاد توجيهها
سرطان الدم اللمفاوي
سرطان الدم اللمفاوي المنتشر كبير الخلايا البائية
متلازمة إطلاق السيتوكين

الملخص

أصبحت الأجسام المضادة ثنائية النوعية CD20×CD3 — إبكوريتاماب وغلوفيتاماب وموسونيتوزوماب وأودرونيكستاماب خيارات علاجية مهمة في حالات مختارة من سرطان الدم اللمفاوي للخلايا البائية الناكس أو المقاوم للعلاج. تستعرض هذه المراجعة السردية أدلة التجارب السريرية حتى أغسطس 2026، مع التركيز على بيانات المرحلة الثالثة العشوائية. في سرطان الدم اللمفاوي المنتشر كبير الخلايا البائية الناكس أو المقاوم للعلاج، حسّن غلوفيتاماب مع العلاج الكيميائي البقيا الكلية مقارنة بالعلاج المناعي الكيميائي في تجربة STARGLO العشوائية (متوسط البقيا الكلية عند 3 سنوات 25.5 مقابل 12.5 شهراً؛ نسبة المخاطرة 0.60)؛ بينما حسّن إبكوريتاماب البقيا الخالية من التطور دون البقيا الكلية مقارنة بالعلاج المناعي الكيميائي في النتائج الأولية لتجربة EPCORE DLBCL-1. وفي سرطان الدم اللمفاوي الجريبي الناكس أو المقاوم للعلاج، حسّنت إضافة إبكوريتاماب إلى لينااليدوميد وريتوكسيماب (R2) البقيا الخالية من التطور (نسبة المخاطرة 0.21) ومعدلات الاستجابة مقارنة بـ R2 وحده في تجربة EPCORE FL-1 العشوائية. وتظهر بيانات المرحلة 2/1 أحادية الذراع نشاطاً ملحوظاً لكن أقل يقيناً لهذه الأدوية ولأودرونيكستاماب في كلا المرضين. تُعد متلازمة إطلاق السيتوكين السمية المبكرة الأبرز، وغالباً ما تكون خفيفة الدرجة مع الجرعات المتدرجة؛ أما متلازمة السمية العصبية المرتبطة بالخلايا

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المناعية الفعالة (ICANS) فهي أقل شيوعاً لكنها ارتبطت بحالات وفاة في مجموعة إبكوريتاماب التسجيلية لعلاج DLBCL. ويبقى خطر العدوى، بما في ذلك العدوى المميتة، ذا أهمية سريرية مع طول مدة العلاج. هذه مراجعة سردية غير منهجية؛ ولا ينبغي قراءة النتائج أحادية الذراع وغير المقارنة على أنها قابلة للمقارنة المباشرة بين الأدوية.

1. Introduction

Relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) is managed with a range of options depending on histology, line of therapy, and fitness, including platinum- or gemcitabine-based salvage chemoimmunotherapy, autologous stem-cell transplantation (ASCT) in transplant-eligible patients, chimeric antigen receptor (CAR) T-cell therapy, antibody-drug conjugates (e.g., polatuzumab ,vedotin, loncastuximab tesirine), and, in follicular lymphoma (FL) lenalidomide-based combinations. CD20×CD3 bispecific antibodies (bsAbs) epcoritamab, glofitamab, mosunetuzumab, and odronextamab are T-cell engagers that simultaneously bind CD20 on malignant B cells and CD3 on cytotoxic T cells. This therapeutic strategy is part of the broader concept of antigen-directed cancer immunotherapy, in which identification of suitable tumour-associated targets is essential for selective immune recognition and therapeutic engagement [1]. These agents have entered the treatment landscape as ,an off-the-shelf option that does not require T-cell collection manufacturing lead time, or lymphodepleting chemotherapy, in .contrast to CAR T-cell therapy [2], [3]

These four agents differ in clinically relevant ways that affect how their trial results should be read. Mosunetuzumab is given as a fixed-duration regimen (up to 8–17 cycles depending on response) with ,treatment stopped after a defined course, whereas epcoritamab glofitamab, and odronextamab are generally given continuously until progression or unacceptable toxicity in their currently reported ,regimens. Epcoritamab is administered subcutaneously; glofitamab .mosunetuzumab, and odronextamab are administered intravenously :Prior exposure to CAR T-cell therapy is an important effect modifier some trial cohorts specifically enrolled CAR-T-naive patients, others enrolled patients after CAR-T failure, and cross-trial comparisons that do not account for this are potentially misleading. Because several randomized trials use different control arms — rituximab-gemcitabine-oxaliplatin (R-GemOx), investigator's choice chemoimmunotherapy (CIT), or lenalidomide-rituximab (R2) a favorable hazard ratio in one trial does not establish superiority over agents or regimens used as comparators in a different trial. The effectiveness of T-cell-directed cancer immunotherapy also depends on appropriate antigen recognition and preservation of functional –cellular immune responses, emphasizing the importance of tumour .host immune interactions in determining therapeutic activity [4]

This review is deliberately restricted to CD20×CD3 T-cell-engaging bsAbs in R/R B-cell lymphoma; CD30×CD16A NK-cell-engaging constructs (e.g., acimtamig/AFM13), used in CD30-positive Hodgkin and T-cell lymphoma, are mechanistically, clinically, and developmentally distinct and are outside this review's scope. The specific question addressed is: has randomized phase 3 evidence, now available for two of these four agents, changed the clinical position of CD20×CD3 bsAbs in R/R DLBCL and FL relative to the earlier single-arm era, and what does this mean for treatment duration, sequencing around CAR T-cell therapy, and infection burden with prolonged exposure? Prior reviews have summarized this drug class [2], [3]; this review's contribution is to synthesize the trial evidence reported or updated through the search date below, with explicit separation of randomized from single-arm evidence and a standardized safety .comparison

2. Review Methods

This is a narrative, non-systematic review. It does not follow PRISMA methodology, did not use dual-reviewer independent screening, and .did not include a formal risk-of-bias assessment or meta-analysis These are acknowledged limitations, stated here for transparency .rather than presented as a systematic review

Literature and regulatory documents were searched in PubMed/MEDLINE, ClinicalTrials.gov, the FDA and EMA websites prescribing information, approval summaries, and European Public) Assessment Reports), and the conference abstract archives of the American Society of Hematology (ASH), American Society of Clinical Oncology (ASCO), and European Hematology Association (EHA). The search covered literature and presentations from January through August 20, 2026 (final search date), applied consistently 2020 across all agents discussed. Search strings combined the agent generic name (epcoritamab, glofitamab, mosunetuzumab, or odronextamab) ,with "lymphoma," "bispecific," and, for safety-focused searches ".cytokine release syndrome," "ICANS," or "infection"

An evidence hierarchy was applied when more than one report existed for the same trial or analysis: final peer-reviewed primary publications ,were used preferentially; where no peer-reviewed publication existed primary regulatory documents (FDA prescribing information/approval summaries, EMA European Public Assessment Reports) or trial registry records were used; conference abstracts were used only where no more mature report was available and are explicitly labeled as such in-text and in the tables; and company press releases were used only as a last resort for topline results not yet reported elsewhere, and are likewise labeled. When multiple reports existed for the same trial (e.g., primary analysis and subsequent long-term follow-up), the most mature available report with the longest follow-up was used as the primary data source, with earlier reports cited only where they add information not superseded by the later report (e.g., STARGLO primary analysis and 3-year follow-up are .(consolidated into a single table row using the latest data cutoff

Eligible reports were phase 1–3 interventional trials of CD20×CD3 bsAbs in patients with B-cell lymphoma reporting at least one efficacy ,endpoint (overall response rate [ORR], complete response [CR] rate progression-free survival [PFS], overall survival [OS], or duration of ,response) or safety endpoint (cytokine release syndrome [CRS] ICANS, infection, cytopenia, treatment discontinuation, or treatment-,related mortality). Preclinical studies, non-English-language reports .and reports without extractable trial-level data were excluded Literature screening and data extraction were performed by a single .reviewer, a further limitation relative to formal systematic review ,Given substantial heterogeneity in trial design, patient populations treatment combinations, and follow-up duration, results are synthesized narratively rather than pooled in a meta-analysis, and cross-trial numerical comparisons are avoided except where explicitly .framed as indirect and non-equivalent

3. CD20×CD3 Bispecifics in Aggressive B-Cell Lymphoma (LBCL/DLBCL)

3.1 Randomized phase 3 evidence

The randomized phase 3 STARGLO trial (n=274) compared glofitamab plus gemcitabine-oxaliplatin (Glofit-GemOx) against rituximab-GemOx (R-GemOx) in transplant-ineligible R/R DLBCL ,after ≥1 prior line. At the latest reported data cutoff (3-year follow-up median 35.1 months), median OS was 25.5 versus 12.5 months (hazard ratio [HR] 0.60, 95% CI 0.43–0.83), median PFS was 14.4 versus 3.3 months (HR 0.41, 95% CI 0.29–0.57), and CR rate was versus 25.3% [5]. This is a single randomized trial against a %58.5 chemoimmunotherapy comparator in a transplant-ineligible population; it does not establish superiority over CAR T-cell therapy .or other salvage strategies not included as comparators

The randomized phase 3 EPCORE DLBCL-1 trial (n=483) compared subcutaneous epcoritamab monotherapy against investigator's choice chemoimmunotherapy (CIT) in R/R DLBCL. Topline results reported a PFS improvement (HR 0.74, 95% CI 0.60–0.92) without a –statistically significant OS improvement (HR 0.96, 95% CI 0.77 As of the search date, this remains a company topline .[6] (1.20 announcement rather than a peer-reviewed or conference-presented primary analysis, which limits independent verification of the reported effect sizes; this should be treated as provisional pending

.fuller reporting

3.2 Single-arm evidence and post-CAR-T activity

In the pivotal single-arm EPCORE NHL-1 trial of subcutaneous epcoritamab monotherapy in R/R LBCL with ≥2 prior therapies (including patients previously treated with CAR T-cell therapy), the registrational efficacy cohort (n=157) showed ORR 59% and CR 41% at 3-year follow-up (median 37.1 months) [7]; the smaller FDA registrational cohort (n=148) reported ORR 61% and CR 38% with median DOR 15.6 months at a median follow-up of 9.8 months among ,responders [8]. A Japanese single-arm cohort (EPCORE NHL-3 .n=36) reported ORR 56% and CR 47% at 3-year follow-up [9]

,In the DLBCL cohort of the phase 2 ELM-2 trial of odronextamab naive to prior CAR T-cell therapy (n=127), the peer-reviewed primary analysis reported ORR 52.0% and CR 31.5%, with median duration of response 10.2 months and median duration of CR 17.9 months at months' efficacy follow-up [10]. Separately, in patients with 29.9 DLBCL specifically progressing after prior CAR T-cell therapy, the phase 1 ELM-1 trial reported ORR 48% and CR 32%, providing direct evidence of post-CAR-T activity for odronextamab, though this is a .smaller, single-arm, non-randomized cohort [11]

4. CD20×CD3 Bispecifics in Follicular Lymphoma

4.1 Randomized phase 3 evidence

The randomized phase 3 EPCORE FL-1 trial compared epcoritamab plus lenalidomide-rituximab (R2) against R2 alone in R/R FL (n=243 vs 245). ORR was 89% versus 74% (p<0.0001) and CR was 74% versus 43% (p<0.0001) favoring the triplet; PFS was not reached with –epcoritamab+R2 versus 11.2 months with R2 (HR 0.21, 95% CI 0.13 This is a chemotherapy-free combination compared against .[12] (0.33 a chemotherapy-free doublet, not against chemoimmunotherapy, and .represents evidence in previously treated rather than untreated FL

4.2 Single-arm and fixed-duration evidence

In the pivotal single-arm phase 2 study of fixed-duration mosunetuzumab monotherapy (up to 8 cycles) in R/R FL after ≥2 prior therapies (n=90), 3-year follow-up (median 37.4 months) showed ORR 77.8% and CR 60.0%, with median PFS 24.0 months; no new CRS events or fatal, serious, or grade ≥3 adverse events emerged with extended follow-up beyond the prior data cutoff [13]. In the non-,randomized US extension cohort of the phase 3 CELESTIMO study mosunetuzumab plus lenalidomide (Mosun-Len) in R/R FL showed ORR 96.3% and CR 87.0% at 12.7 months' follow-up; this is an uncontrolled cohort reported at a conference, not yet published as a .peer-reviewed randomized comparison [14]

In the FL cohort of ELM-2 (n=128), the peer-reviewed primary analysis reported ORR 80.0% (95% CI 72.5–86.9%) and CR 73.4% at 20.1 months' median follow-up, with median duration of CR 25.1 months [15]; a corrigendum to this publication corrected a dosing-regimen typographical error in the supplementary material without .altering the reported efficacy or safety results [16]

Table 1. Summary of Principal Efficacy Trials (randomized evidence listed first within each disease setting)

Trial (Agent)	Design	Setting / Comparator	N	ORR (95% CI)	CR	PFS / OS (HR, 95% CI)	DOR / DOCR	Follow-up
STARGLO (Glofit-GemOx) [5]	Ph3 RCT	R/R DLBCL vs R-GemOx	274	NR	58.5% vs 25.3%	OS HR 0.60 (0.43-0.83); PFS HR 0.41 (0.29-0.57)	NR	35.1 mo
EPCORE DLBCL-1 (Epcoritamab) [6]*	Ph3 RCT (topline)	R/R DLBCL vs CIT	483	NR	NR	PFS HR 0.74 (0.60-0.92); OS HR 0.96 (0.77-1.20), ns	NR	NR
EPCORE NHL-1 (Epcoritamab) [7]	Ph1/2, single-arm	R/R LBCL, ≥2 prior lines	157	59%	41%	n/a (single-arm)	NR	37.1 mo
EPKINLY label cohort (Epcoritamab) [8]	Ph1/2, single-arm (regulatory)	R/R LBCL/DLBCL, ≥2 prior lines	148	61% (53-69)	38%	n/a (single-arm)	mDOR 15.6 mo	9.8 mo (responders)
EPCORE NHL-3 (Epcoritamab) [9]	Ph1/2, single-arm	R/R DLBCL, Japan	36	56%	47%	n/a (single-arm)	NR	36.7 mo
ELM-2 DLBCL (Odronextamab) [10]	Ph2, single-arm	R/R DLBCL, CAR-T naive	127	52.0%	31.5%	n/a (single-arm)	mDOR 10.2 mo; mDOR-CR 17.9 mo	29.9 mo
ELM-1 post-CAR-T (Odronextamab) [11]	Ph1, single-arm	R/R DLBCL, post-CAR-T progression	NR	48%	32%	n/a (single-arm)	NR	NR
EPCORE FL-1 (Epcoritamab+R2) [12]	Ph3 RCT	R/R FL, epcor+R2 vs R2	243 vs 245	89% vs 74%	74% vs 43%	PFS HR 0.21 (0.13-0.33); mPFS NR vs 11.2 mo	NR	NR
Mosunetuzumab monotherapy [13]	Ph2, single-arm, fixed-duration	R/R FL, ≥2 prior lines	90	77.8%	60.0%	n/a (single-arm)	mPFS 24.0 mo	37.4 mo
CELESTIMO US ext. (Mosun-Len) [14]*	Ph3, single-arm cohort (abstract)	R/R FL	NR	96.3%	87.0%	n/a (uncontrolled)	NR	12.7 mo
ELM-2 FL (Odronextamab) [15,16]	Ph2, single-arm	R/R FL, ≥2 prior lines	128	80.0% (72.5-86.9)	73.4%	n/a (single-arm)	mDOR-CR 25.1 mo	20.1 mo

Company topline or conference-abstract source (not yet peer-* ;reviewed); see evidence hierarchy in Section 2. NE: not estimable NR: not reported/not reached; CIT: chemoimmunotherapy ;(investigator's choice); R2: lenalidomide plus rituximab ;mDOR/mDOR-CR: median duration of response/complete response .ns: not statistically significant

5. Safety and Implementation

,Table 2 standardizes safety data using consistent categories (CRS ICANS, infection, neutropenia, discontinuation, treatment-related death) across trials, with the grading system and population ;(monotherapy, combination, or pooled cohort) specified for each row qualitative labels such as “rare” or “low” are avoided in favor of exact .reported percentages where available

CRS is the most common early toxicity of CD20×CD3 bsAbs and is concentrated in the first 1–2 treatment cycles across agents. In the EPCORE NHL-1 registrational LBCL cohort, CRS occurred in 51% of patients (37% grade 1, 17% grade 2, 2.5% grade 3) [8]. ICANS, a distinct and separately graded toxicity from CRS, occurred less frequently but is clinically important: ICANS was included among serious adverse reactions occurring in ≥2% of patients and among fatal adverse reactions (0.6%) in the same registrational population This exact incidence and severity distribution, rather than a .[8] qualitative descriptor, should be used when characterizing .epcoritamab's neurotoxicity profile in this population

In cohorts using optimized step-up dosing regimens for example, the mg odronextamab regimen or epcoritamab's cycle-1 dose- 20/4/0.7 optimization schedule CRS incidence and severity were lower than in earlier, non-optimized cohorts within the same development programs. Because these are before/after or across-cohort comparisons rather than randomized comparisons, this should be described as an observed association with lower incidence rather than .a proven causal reduction

Infection is a persistent risk with prolonged CD20×CD3 bsAb exposure, reflecting sustained B-cell depletion and consequent hypogammaglobulinemia; this immunologic consequence is distinct ,from hematologic cytopenias (neutropenia, anemia thrombocytopenia) and both should be tracked separately from CRS/ICANS. In the ELM-2 DLBCL cohort, grade ≥3 infections occurred in 37% of patients, including 11% grade 5 (fatal) infections in the pooled ELM-1/ELM-2 population, COVID-19 infection ;[10] was a specific and clinically significant contributor to infection-related mortality. "No new adverse events" reported at long-term follow-up (e.g., mosunetuzumab 3-year data) means no new events emerged after the prior data cutoff; it does not mean serious or grade events did not occur earlier in the same trial, and should not be read 3≤ .as an overall safety guarantee

Practically, fixed-duration regimens (mosunetuzumab) limit cumulative infection and hypogammaglobulinemia exposure by ,design, while continuously dosed regimens (epcoritamab, glofitamab odronextamab in their currently reported schedules) require ongoing monitoring for infection and consideration of immunoglobulin replacement or antimicrobial/antiviral prophylaxis with prolonged exposure; head-to-head data comparing these strategies are not yet .available

Table 2. Standardized Safety Profile by Trial (CRS and ICANS reported separately; infection separated from hematologic and immunologic toxicity)

Trial (Agent)	Population / N	Grading	CRS any / ≥3	ICANS any / ≥3 / Gr5	Infection ≥3 / fatal	Neutropenia ≥3	Discontinuation (AE)	Treatment-related death
STARGLO (Glofit-GemOx) [5]	R/R DLBCL, n=274, combo	NR	44% / ~2-3%	NR	NR	NR	NR	3% (vs 1% R-GemOx)
EPKINLY label (Epcoritamab) [8]	R/R LBCL, n=157, monoRx	ASTCT (label)	51% / 2.5%	Incl. in serious AR ≥2%; fatal AR 0.6%	Fatal AR: COVID-19 1.3%	NR	3.8%	3.8% (all fatal AR)
EPCORE FL-1 (Epcoritamab+R2) [12]	R/R FL, combo	NR	24% (19% G1, 5% G2)	1/243 (0.8%, Gr1)	NR	Gr3/4 lab abn. ≥10%	NR	NR
ELM-2 DLBCL (Odronextamab) [10]	R/R DLBCL, n=127 (n=141 safety), monoRx	NR	55% (98% G1/2 w/ optimized step-up)	0% with optimized step-up regimen	37% / 11% (Gr5)	NR	NR	Included in infection deaths above
Pooled ELM-2 FL, optimized [15]	R/R FL, step-up regimen	NR	Mostly G1/2 (36% G1, 19% G2)	0 events reported with optimized regimen	NR	NR	NR	1 pt Gr≥3 CRS (confounded by pancreatitis)
Mosunetuzumab monotherapy [13]	R/R FL, n=90, fixed-duration monoRx	NR	Predominantly low-grade, cycle 1; none new at 3-yr	None new at 3-yr follow-up	NR	NR	NR	None new at 3-yr follow-up
CELESTIMO US ext. (Mosun-Len) [14]	R/R FL, combo cohort (abstract)	NR	27.8% (22.2% G1, 3.7% G2, 1.9% G3)	NR	57.4% any-grade (COVID-19 20.4%)	33.3% (Gr3/4)	NR	1 fatal AE (pneumonia)

:AR: adverse reaction (FDA labeling term); AE: adverse event; Gr grade; ASTCT: American Society for Transplantation and Cellular Therapy consensus grading. Where a specific grading system was not .stated in the source, this is marked NR rather than assumed

6. Regulatory Status

As of the search date, epcoritamab (Epkinly) and glofitamab hold FDA accelerated approval and EMA authorization for R/R DLBCL after ≥2 prior lines, with epcoritamab additionally approved in ;combination with R2 for R/R FL following the EPCORE FL-1 results ,mosunetuzumab holds approval for R/R FL after ≥2 prior lines [2, 8 .[13 ,12

Odronextamab's regulatory history is more complex and region-specific. The European Commission granted conditional marketing authorization for odronextamab (Ordspono) for R/R FL and R/R DLBCL after ≥2 prior lines in August 2024, following a positive CHMP opinion on 27 June 2024, based on the ELM-1 and ELM-2 trials [17]. In the United States, the FDA issued a complete response letter (CRL) in March 2024 related to enrollment status of the confirmatory phase 3 trial, not to efficacy, safety, trial design, or manufacturing [18]. Following attainment of the relevant enrollment target, a BLA resubmission for the FL indication was accepted in February 2025 with a PDUFA target date of July 30, 2025; the FDA subsequently issued a second CRL for the FL indication related to observations from a general site inspection at a third-party manufacturing facility, not to efficacy or safety of odronextamab itself As of this review's search date, odronextamab therefore remains .[19] .approved in the EU but not yet approved in the US

7. Discussion

Randomized phase 3 evidence is now available for two of the four CD20×CD3 bsAbs discussed here, in specific settings: glofitamab plus chemotherapy improved OS versus chemoimmunotherapy in transplant-ineligible R/R DLBCL (STARGLO), and epcoritamab plus R2 improved PFS and response rates versus R2 alone in previously treated FL (EPCORE FL-1). Epcoritamab's DLBCL-1 topline results improved PFS but not OS versus chemoimmunotherapy, and remain -unpublished beyond a company announcement. These are agent-, trial and setting-specific findings and do not establish class-wide , ,superiority of CD20×CD3 bsAbs over other treatment strategies including CAR T-cell therapy, which was not a comparator arm in any .of the trials reviewed here

On sequencing relative to CAR T-cell therapy: available data indicate that CD20×CD3 bsAbs retain meaningful activity after CAR-T failure ELM-1 post-CAR-T cohort, ORR 48%; EPCORE NHL-1 included) CAR-T-pretreated patients within its overall 59% ORR), supporting their use as a subsequent-line, off-the-shelf option without the ,manufacturing delay of a second CAR-T product. Conversely whether bsAb exposure affects the efficacy of a subsequent CAR-T attempt — through T-cell exhaustion or antigen-escape mechanisms is not well characterized in the trials reviewed and represents an .important gap given the increasing use of both modalities in sequence

On treatment duration: mosunetuzumab's fixed-duration design (up to cycles) is a structurally different exposure strategy from the 8 continuous dosing used in the epcoritamab, glofitamab, and odronextamab regimens reported here, with plausible implications for cumulative infection risk, hypogammaglobulinemia, cost, and patient burden; however, no trial in this review directly randomized fixed-duration against continuous dosing, so this remains a hypothesis-generating observation rather than an established comparative .advantage

On resistance and biomarkers: CD20 loss or antigenic downregulation, T-cell dysfunction or exhaustion after prolonged engager exposure, and tumor microenvironmental factors have been ,proposed as mechanisms of acquired resistance to CD20×CD3 bsAbs though the trials reviewed here were not designed to characterize resistance mechanisms directly. This underscores the general importance of sustained tumour-associated antigen expression for the success of antigen-directed therapies: reduced or lost CD20 expression removes the target that these bsAbs depend on, echoing the

broader principle that identification and persistence of a suitable tumour-associated target is a prerequisite for durable immune-mediated tumour control [1]. Preservation of functional T-cell responses is equally relevant, since bsAb activity depends on host cytotoxic T cells remaining capable of recognizing and eliminating antigen-bearing tumour cells rather than on an engineered cellular product, linking durability of response to the broader tumour–host immune interaction [4]. Minimal residual disease (MRD) status by circulating tumor DNA was associated with PFS in exploratory ELM-analyses [10], suggesting a possible role for MRD-guided treatment 2 duration or discontinuation decisions; prospective validation is .needed before this can inform practice

On infection burden specifically: the combination of grade ≥3 infection rates in the range of one-third of patients and infection-related fatal events (including COVID-19) in some cohorts represents a clinically important, not merely theoretical, risk that should be ,weighed against the convenience of an off-the-shelf agent particularly in older or more heavily pretreated patients, and argues for systematic infection-prophylaxis strategies as these regimens .move into earlier lines of therapy

Limitations of the evidence base, and of this review, include: this is a narrative rather than formal systematic review without dual-reviewer screening or risk-of-bias assessment; most included trials outside STARGLO and EPCORE FL-1 are single-arm phase 1/2 studies without concurrent controls; EPCORE DLBCL-1 is available only as a company topline announcement at the time of this review; cross-trial ,heterogeneity in patient populations, prior therapy exposure CRS/ICANS grading conventions, and prophylaxis protocols limits direct comparison even where numerical results are presented together; and follow-up remains comparatively short for several .combination and frontline regimens

8. Conclusion

Within the above limitations, randomized phase 3 evidence now supports specific benefits for CD20×CD3 bsAbs in defined R/R settings glofitamab plus chemotherapy for OS in transplant-ineligible R/R DLBCL (STARGLO), and epcoritamab plus R2 for PFS and response in previously treated FL (EPCORE FL-1). Evidence for odronextamab, for mosunetuzumab combinations, and for ,epcoritamab in DLBCL-1 remains either single-arm ,topline/unpublished, or based on non-randomized extension cohorts and should be described accordingly rather than placed on equal evidentiary footing with the randomized results. CRS is well characterized and appears reducible with step-up dosing in non-randomized comparisons; ICANS and infection, including fatal ,infection, are less frequent but clinically important and require exact trial-specific reporting rather than qualitative reassurance. The most important unresolved clinical questions are how to sequence CD20×CD3 bsAbs around CAR T-cell therapy, whether fixed-duration and continuous-dosing strategies produce meaningfully different long-term infection and efficacy outcomes, what resistance mechanisms limit durability, and whether MRD-guided approaches .can safely inform treatment duration

9. Abbreviations and Acronyms

ASCT: autologous stem-cell transplantation; bsAb: bispecific antibody; CI: confidence interval; CIT: chemoimmunotherapy (investigator's choice); CR: complete response; CRL: complete response letter; CRS: cytokine release syndrome; DLBCL: diffuse ;large B-cell lymphoma; DOR/mDOR: (median) duration of response mDOR-CR: median duration of complete response; FL: follicular lymphoma; HR: hazard ratio; ICANS: immune effector cell-;associated neurotoxicity syndrome; ICR: independent central review ;IRC: independent review committee; LBCL: large B-cell lymphoma ;NE: not estimable; NHL: non-Hodgkin lymphoma; NR: not reported ORR: overall response rate; OS: overall survival; PFS: progression-free survival; R/R: relapsed/refractory; R2: lenalidomide plus .rituximab; R-GemOx: rituximab plus gemcitabine-oxaliplatin

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.AI tool used: Claude (Anthropic), accessed via Claude.ai

Task performed: The AI tool was used to conduct literature and regulatory-document searches, and to draft and organize the synthesized manuscript text, tables, and reference list, including .revisions responding to editorial and peer review

Author confirmation: The author has reviewed, verified against ,original sources, and edited the AI-assisted output for accuracy completeness, and potential bias, and takes full responsibility for the .content, interpretation, and conclusions of this manuscript

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