Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma.

Michael J. Dickinson, Carmelo Carlo-Stella, Franck Morschhauser, Emmanuel Bachy, Paolo Corradini, Gloria Iacoboni, Cyrus Khan, Tomasz Wróbel, Fritz Offner, Marek Trněný, et al.

ORIGINAL ARTICLE

Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Michael J. Dickinson, M.B., B.S., D.Med.Sc., Carmelo Carlo-Stella, M.D., Franck Morschhauser, M.D., Ph.D., Emmanuel Bachy, M.D., Ph.D., Paolo Corradini, M.D., Gloria Iacoboni, M.D., Cyrus Khan, M.D., Tomasz Wróbel, M.D., Fritz Offner, M.D., Ph.D., Marek Trněný, M.D., Shang-Ju Wu, M.D., Ph.D., Guillaume Cartron, M.D., Ph.D., Mark Hertzberg, M.B., B.S., Ph.D., Anna Sureda, M.D., Ph.D., David Perez-Callejo, Ph.D., Linda Lundberg, Ph.D., James Relf, M.D., Mark Dixon, M.Sc., Emma Clark, M.Sc., Kathryn Humphrey, B.Sc., and Martin Hutchings, M.D., Ph.D.

ABSTRACT

BACKGROUND

The prognosis for patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) is poor. Glofitamab is a bispecific antibody that recruits T cells to tumor cells.

METHODS

In the phase 2 part of a phase 1–2 study, we enrolled patients with relapsed or refractory DLBCL who had received at least two lines of therapy previously. Patients received pretreatment with obinutuzumab to mitigate cytokine release syndrome, followed by fixed-duration glofitamab monotherapy (12 cycles total). The primary end point was complete response according to assessment by an independent review committee. Key secondary end points included duration of response, survival, and safety.

RESULTS

Of the 155 patients who were enrolled, 154 received at least one dose of any study treatment (obinutuzumab or glofitamab). At a median follow-up of 12.6 months, 39% (95% confidence interval [CI], 32 to 48) of the patients had a complete response according to independent review. Results were consistent among the 52 patients who had previously received chimeric antigen receptor T-cell therapy (35% of whom had a complete response). The median time to a complete response was 42 days (95% CI, 42 to 44). The majority (78%) of complete responses were ongoing at 12 months. The 12-month progression-free survival was 37% (95% CI, 28 to 46). Discontinuation of glofitamab due to adverse events occurred in 9% of the patients. The most common adverse event was cytokine release syndrome (in 63% of the patients). Adverse events of grade 3 or higher occurred in 62% of the patients, with grade 3 or higher cytokine release syndrome in 4% and grade 3 or higher neurologic events in 3%.

CONCLUSIONS

Glofitamab therapy was effective for DLBCL. More than half the patients had an adverse event of grade 3 or 4. (Funded by F. Hoffmann–La Roche; ClinicalTrials.gov number, NCT03075696.)

The authors' affiliations are listed in the Appendix. Dr. Dickinson can be contacted at michael.dickinson@petermac.org or at the Peter MacCallum Cancer Centre, 305 Grattan St., Melbourne, VIC 3000, Australia.

This article was published on December 11, 2022, at NEJM.org.

N Engl J Med 2022;387:2220-31.
DOI: 10.1056/NEJMoa2206913

CME at NEJM.org

Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the standard first-line treatment for diffuse large B-cell lymphoma (DLBCL).[1] However, 35 to 40% of patients have a relapse or have disease that is refractory to R-CHOP.[1] Among patients with DLBCL who are considered to be eligible candidates for autologous stem-cell transplantation, 60% do not proceed to transplantation after the receipt of salvage chemotherapy[2] or have a relapse shortly after the procedure.[3-6] The prognosis is poor for patients who are unsuitable candidates for second-line treatment with aggressive salvage chemotherapy and for those who have received at least two therapies previously.[3,7-9]

Treatments that have been approved for relapsed or refractory DLBCL[10] after the receipt of at least two lines of therapy include antibody–drug conjugates,[11,12] tafasitamab with lenalidomide,[13] pixantrone,[14] selinexor,[15] and chimeric antigen receptor (CAR) T-cell therapies (e.g., axicabtagene ciloleucel [axi-cel],[16] tisagenlecleucel [tisa-cel],[17] and lisocabtagene maraleucel [liso-cel]).[18] Although CAR T-cell therapies appear to be the most effective, they are not consistently available owing to logistic, geographic, or resourcing constraints. Not all patients who are selected to receive CAR T-cell infusion actually do so because of disease progression or death while awaiting therapy,[19-21] and only approximately 40% of patients have durable remission with third-line CAR T-cell therapy.[22] Hence, effective and immediately available treatments are needed. To address this need, we evaluated the new T-cell–engaging bispecific antibody glofitamab.

Glofitamab is distinct in the emerging class of CD20×CD3 bispecific monoclonal antibodies because it has a novel 2:1 tumor–T-cell binding configuration that confers bivalency for CD20 (B cells) and monovalency for CD3 (T cells), leading to the engagement and redirection of patients' existing T cells to eliminate malignant B cells.[23] Having established a recommended phase 2 dose of glofitamab, with obinutuzumab pretreatment to mitigate cytokine release syndrome,[24] we enrolled expansion cohorts of patients with DLBCL who had received at least two lines of therapy previously.

METHODS

STUDY OVERSIGHT

We enrolled patients with relapsed or refractory DLBCL who had received at least two lines of previous therapy into the phase 2 part of an open-label phase 1–2 clinical trial. The study was designed by the sponsor (F. Hoffmann–La Roche) with the lead investigators (the first, third, and last authors). The design of the dose-expansion cohort is described in the study protocol, which is available with the full text of this article at NEJM.org. The dose-escalation part of this study has been published previously.[24]

The protocol was approved by the institutional review board at each center. The study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines of the International Council for Harmonisation, and applicable laws. Data were collected by the investigators, analyzed by statisticians employed by the sponsor, and interpreted by all the authors. The authors vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol. Medical writing assistance (development of the first manuscript draft and editorial assistance with subsequent drafts) was provided under the direction of all the authors and funded by the sponsor. All the authors participated in the preparation and approval of the final manuscript draft for submission.

PATIENTS

Patients 18 years of age or older who had histologically confirmed DLBCL (not otherwise specified), transformed follicular lymphoma, high-grade B-cell lymphoma, or primary mediastinal large B-cell lymphoma and an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher numbers indicating greater disability) were included. All the patients had disease that had relapsed after, or was refractory to, at least two previous lines of therapy including at least one anti-CD20 antibody-containing regimen and at least one anthracycline-containing regimen. Key eligibility criteria are listed in the Supplementary Appendix, available at NEJM.org. All the participants provided written informed consent.

A Quick Take is available at NEJM.org

STUDY TREATMENT

Pretreatment with obinutuzumab (1000 mg) was administered intravenously 7 days before the first dose of glofitamab. Glofitamab was then administered intravenously as step-up doses on day 8 (2.5 mg) and day 15 (10 mg) of cycle 1, followed by a dose of 30 mg on day 1 of cycles 2 through 12 (cycles lasted 21 days); this constituted the previously established phase 2 dose. Patients were hospitalized for receipt of the first dose of glofitamab; hospitalization requirements evolved during the study, such that subsequent doses were administered in the outpatient setting unless cytokine release syndrome of grade 2 or higher was reported after the first dose. Patients were treated for 12 cycles or until the occurrence of disease progression or an unacceptable level of toxic effects. Details of premedications that were administered to reduce infusion-related reactions and cytokine release syndrome events related to treatment are provided in the protocol. Details of requirements regarding glucocorticoid treatment are also provided in the Supplementary Appendix.

ASSESSMENTS

Tumor assessment on computed tomography (CT) and positron-emission tomography (PET)–CT was performed at screening; after cycles 2, 5, and 8; at the end of treatment; and every 6 months until disease progression occurred. Responses were assessed on PET-CT scans by the investigator and by an independent review committee using the Lugano response criteria.[25]

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, of the National Cancer Institute.[26] In accordance with the protocol, cytokine release syndrome was graded according to the 2014 criteria of Lee et al.[27] Grades according to the American Society for Transplantation and Cellular Therapy (ASTCT) were derived from the reported symptoms and treatments.[28] The criteria for the immune effector cell–associated neurotoxicity syndrome (ICANS) were not used at the time of study initiation; events were described on the basis of CTCAE terms consistent with ICANS.[28]

STUDY OUTCOMES

The primary efficacy end point was complete response as assessed by the independent review committee.[25] We report the percentage of patients whose best overall response was a complete response. Patients with missing or no response assessments were classified as not having a response. Secondary efficacy end points included complete response according to investigator assessment, objective response (complete or partial response), duration of response, duration of complete response, time to first complete response, and time to first objective response (all assessed by both the independent review committee and the investigator), as well as progression-free survival and overall survival. Definitions of key time-to-event efficacy end points are provided in the Supplementary Appendix.

ANALYSIS COHORTS

The main analysis included all the patients who were intended to be treated at the established phase 2 dose, including those in the dose-escalation part of the study. The study also included a pivotal cohort with a target sample size to enable a statistical test of the study hypothesis, as well as a mandatory dexamethasone cohort, which was designed to evaluate the effect of consistent use of this glucocorticoid on toxic effects, given that it has the longest half-life of the glucocorticoids that were used as premedication across the study.

A supporting cohort, separate from the main analysis cohort, was evaluated to provide additional evidence on the durability of complete response after glofitamab treatment. We analyzed this outcome in patients meeting the same inclusion and exclusion criteria as the patients in the main analysis cohort. These patients had been treated with glofitamab doses of 10 mg or higher but lower than the phase 2 dose; such patients may have received fixed doses of glofitamab at 10 mg, 16 mg, or 25 mg; a single step of 10 mg followed by 16 mg; or two steps of 2.5 mg and 10 mg followed by 16 mg. In this cohort, the treatment duration was 8 to 12 cycles.

STATISTICAL ANALYSIS

We calculated that the pivotal cohort would need a target sample size of 100 in order to provide the study with 92% power to detect an increase from 20% to 35% in the percentage of patients with a complete response, at a two-sided alpha level of 5%. The observed percentage of patients with a complete response in the intention-to-

treat population (which included all the patients enrolled in this cohort) was compared with a prespecified value of 20% (for complete response in a historical control), which was established on the basis of a meta-analysis of 19 studies, with the use of an exact binomial test.

All the patients in the main analysis cohort who received obinutuzumab or glofitamab were included in the safety population. We used the Clopper–Pearson method to calculate 95% confidence intervals for the percentages of patients with a response. Kaplan–Meier plots were calculated for survival end points. The confidence intervals were not adjusted for multiplicity and should not be interpreted as hypothesis tests. Prespecified subgroup analyses of the primary end point were performed. Efficacy analyses were performed in the intention-to-treat population. Data were analyzed with the use of SAS software, version 9.4 (SAS Institute). A data-cutoff date of March 14, 2022, was used.

RESULTS

PATIENTS

From January 2020 through September 2021, a total of 155 patients were enrolled to receive glofitamab monotherapy at the phase 2 dose (step-up doses of 2.5 mg and 10 mg, followed by 30 mg on day 1 of cycles 2 through 12). One patient was enrolled in error (did not undergo screening and did not receive study treatment). Therefore, 154 patients received at least one dose of any study treatment (obinutuzumab or glofitamab; safety population) (Fig. S1). The main analysis included 108 patients in the pivotal cohort, 40 in the mandatory dexamethasone cohort, and 7 patients who had been treated at the phase 2 dose in the dose-escalation part of the study. In addition, 101 patients were in the supporting cohort, receiving glofitamab at a dose of 10 mg or higher but below the phase 2 dose.

At the data-cutoff date (March 14, 2022), a total of 34 patients (22%) had completed the planned full course of treatment, 12 (8%) were actively receiving treatment, and 108 (70%) had discontinued treatment. The predominant reason for treatment discontinuation was progressive disease.

A total of 12 patients discontinued treatment while they were having a complete response according to assessment by the independent review committee. Three of these patients discontinued owing to investigator-assessed progressive disease. Among the remaining 9 patients, discontinuation was due to physician decision (in 7 patients), an adverse event (grade 4 neutropenia in 1 patient), and an unknown reason (in 1 patient). Eight of these 9 patients received consolidation therapy; 7 underwent allogeneic stem-cell transplantation, and 1 received CAR T-cell therapy. The patient who discontinued owing to neutropenia was in remission as of the 24-month follow-up visit.

Overall, 110 patients (71%) had DLBCL (not otherwise specified), 27 (18%) had transformed follicular lymphoma, 11 (7%) had high-grade B-cell lymphoma, and 6 (4%) had primary mediastinal large B-cell lymphoma. The median age of the patients was 66 years (range, 21 to 90). Patients had received a median of three lines (range, two to seven) of therapy previously. A total of 60% of the patients had received at least three previous therapies, and 33% had received CAR T-cell therapy previously (85% had received commercially available CAR T cells, and 15% CAR T-cell therapy that was not specified or that was part of a clinical trial; 83% had received CAR T-cell therapy at a second or subsequent relapse, and 17% at first relapse). Among the patients who had received CAR T-cell therapy previously, 71% had received it as the therapy immediately preceding study enrollment, and 89% had disease that was refractory to it. The median duration between the receipt of CAR T-cell therapy and obinutuzumab pretreatment was 127 days (range, 46 to 912; interquartile range, 104 to 212). Most patients had advanced disease (Ann Arbor stage III or IV disease in 75%) and had disease that was refractory to previous treatment (primary refractory in 58% of the patients and refractory to last therapy in 86%) (Table 1).

The median duration of glofitamab treatment was 79 days (range, 1 to 326). The median number of glofitamab cycles received was 5 (range, 1 to 13). Patients with a complete response received a median of 12 cycles. All the patients had a dose intensity of at least 90%.

The population in this study was representative, with respect to age and sex, of a typical population of patients with DLBCL (Table S1). The study was conducted primarily in Europe

Table 1. Demographic and Clinical Characteristics at Baseline of All 154 Patients Treated at the Phase 2 Dose (Safety Population).*

Characteristic	Value
Median age (range) — yr	66 (21–90)
Male sex — no. (%)	100 (65)
ECOG performance-status score — no. (%)†	
0	69 (45)
1	84 (55)
Ann Arbor stage at time of study entry — no. (%)	
I	10 (6)
II	25 (16)
III	31 (20)
IV	85 (55)
Missing data	3 (2)
Non-Hodgkin's lymphoma subtype — no. (%)	
Diffuse large B-cell lymphoma, not otherwise specified	110 (71)
Transformed follicular lymphoma	27 (18)
High-grade B-cell lymphoma	11 (7)
Primary mediastinal B-cell lymphoma	6 (4)
Bulky disease at study entry	
>6 cm	64 (42)
>10 cm	18 (12)
Previous lines of therapy	
Median no. of lines (range)	3 (2–7)
Only 2 previous lines — no. (%)	62 (40)
≥3 previous lines — no. (%)	92 (60)
Previous therapy for lymphoma — no. (%)	
Anti-CD20 antibody	154 (100)
Anthracycline	149 (97)
CAR T-cell therapy	51 (33)
Autologous stem-cell transplantation — no. (%)	28 (18)
Relapsed or refractory status — no. (%)‡	
Refractory to any previous therapy	139 (90)
Refractory to last previous therapy	132 (86)
Primary refractory	90 (58)
Refractory to any previous anti-CD20 therapy	128 (83)
Refractory to previous CAR T-cell therapy	46 (30)

* The safety population included all the patients who received at least one dose of study treatment (obinutuzumab or glofitamab). Glofitamab was then administered intravenously as step-up doses on day 8 (2.5 mg) and day 15 (10 mg) of cycle 1, followed by a dose of 30 mg on day 1 of cycles 2 through 12 (phase 2 dose). Percentages may not total 100 because of rounding. CAR denotes chimeric antigen receptor.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores are on a 5-point scale, with higher numbers indicating greater disability. A score of 0 indicates that the patient is fully active and able to carry on all predisease performance without restriction, and a score of 1 that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work). At baseline, one patient had a score of 2, indicating that the patient was capable of all self-care and was up and about more than 50% of waking hours but was unable to carry out any work activities. Although the patient was eligible at trial enrollment (ECOG performance-status score of 1), the patient's performance status deteriorated before the receipt of study treatment.

‡ Refractory disease was defined in patients who had no response, progression, or relapse within 6 months after the end date of the first therapy for lymphoma.

and Australia, predominantly at academic institutions. Such settings may have limited the racial diversity of patients with relapsed and refractory DLBCL as compared with the general population in those regions and worldwide. The follow-up of the 108 patients in the pivotal cohort is shown in Figure S2, with the demographic and clinical characteristics of these patients listed in Table S2.

EFFICACY

At a median follow-up of 12.6 months (range, 0.1 to 22.1) among the 155 patients who received the phase 2 dose of glofitamab, 39% of the patients (95% confidence interval [CI], 32 to 48) had a complete response (as the best response) as assessed by the independent review committee (Table 2). A total of 52% of the patients (95% CI, 43 to 60) had an objective response. (Corresponding data regarding the pivotal cohort are provided in Table S3.) Concordance between results according to independent-review assessment and investigator assessment was 93% for complete response and 86% for objective response.

The median time to a complete response according to assessment by the independent review committee was 42 days (95% CI, 42 to 44), which correlated with the first scheduled response assessment (at approximately 1.4 months). Between day 1 of cycle 3 and day 1 of cycle 6, a total of 6 patients with a partial response had conversion to a complete response, and 8 patients with a partial response had conversion to progressive disease.

At the time of the primary analysis in the pivotal cohort (September 14, 2021), with a median follow-up of 9.0 months (range, 0.1 to 16.0), 38 of 108 patients (35%; 95% CI, 26 to 45) had a complete response according to assessment by the independent review committee; this percentage was significantly higher than the 20% observed in a historical control cohort ($P<0.001$). In the main analysis cohort, prespecified subgroup analyses of complete response according to the independent review committee showed consistency of the treatment effect among patients who had received previous CAR T-cell therapy and those who had not (35% and 42%, respectively) and among patients younger than 65 years of age and those 65 years of age or older (Fig. 1). Subgroups involving patients with relapsed disease showed a trend toward a higher percentage with a complete response, as com-

Table 2. Efficacy According to Independent Review Committee and Investigator Assessment (Intention-to-Treat Population).*

Outcome	Assessment According to Independent Review Committee (N=155)	Assessment According to Investigator (N=155)
Complete response		
No. of patients with response	61	58
Percentage of patients (95% CI)	39 (32–48)	37 (30–46)
Objective response		
No. of patients with response	80	89
Percentage of patients (95% CI)	52 (43–60)	57 (49–65)
Duration of complete response†		
Median (95% CI) — mo	NR (16.8–NR)	19.8 (18.2–NR)
Complete response at 12 mo (95% CI) — %	78 (64–91)	72 (59–86)
Duration of objective response‡		
Median (95% CI) — mo	18.4 (13.7–NR)	10.4 (6.8–NR)
Objective response at 12 mo (95% CI) — %	64 (51–76)	49 (37–61)
Median time to first complete response (range) — days†	42 (31–308)	43 (31–274)
Progression-free survival		
Median (95% CI) — mo	4.9 (3.4–8.1)	3.8 (3.3–5.4)
Alive without progression at 12 mo (95% CI) — %	37 (29–46)	30 (22–38)
Overall survival		
Median (95% CI) — mo	—	11.5 (7.9–15.7)
Alive at 12 mo (95% CI) — %	—	50 (41–58)

* The intention-to-treat population included all the patients enrolled in the study. The primary outcome was complete response as assessed by the independent review committee. Patients were included in the analyses of complete or objective (i.e., complete or partial) response on the basis of their best response to glofitamab therapy, as assessed by the independent review committee or the investigator. NR denotes not reached.
† The median duration of complete response and the median time to the first complete response were assessed only among patients with a complete response.
‡ The median duration of objective response was assessed only among patients who had a complete or partial response.

pared with subgroups involving patients with refractory disease (Fig. 1). Complete response was observed in patients regardless of histologic category, except among those with high-grade B-cell lymphoma (among 11 treated patients, 2 had a partial response). Prespecified subgroup analyses of complete response in the pivotal cohort showed similar trends (Fig. S3).

At the data-cutoff date, 66% of the objective responses (in 53 of 80 patients) and 80% of the complete responses (in 49 of 61 patients) were ongoing. The median duration of objective response was 18.4 months (95% CI, 13.7 to not reached). Objective response was ongoing at 12 months in 64% (95% CI, 51 to 76) of the 80 patients with an objective response (Table 2 and Fig. S4). The median duration of complete response was not reached (95% CI, 16.8 to not reached). Complete response was ongoing at 12 months in 78% (95% CI, 64 to 91) of the 61 patients with a complete response (Table 2 and Fig. 2). (Corresponding data for the pivotal cohort are shown in Fig. S5.)

In the intention-to-treat population, the 6-month progression-free survival was 46% (95% CI, 37 to 54), and the 12-month progression-free survival was 37% (95% CI, 28 to 46). Overall, the median progression-free survival as assessed by the independent review committee was 4.9 months (95% CI, 3.4 to 8.1) (Table 2 and Fig. 2). The estimated 12-month overall survival among all 155 patients was 50% (95% CI, 41 to 58) (Fig.

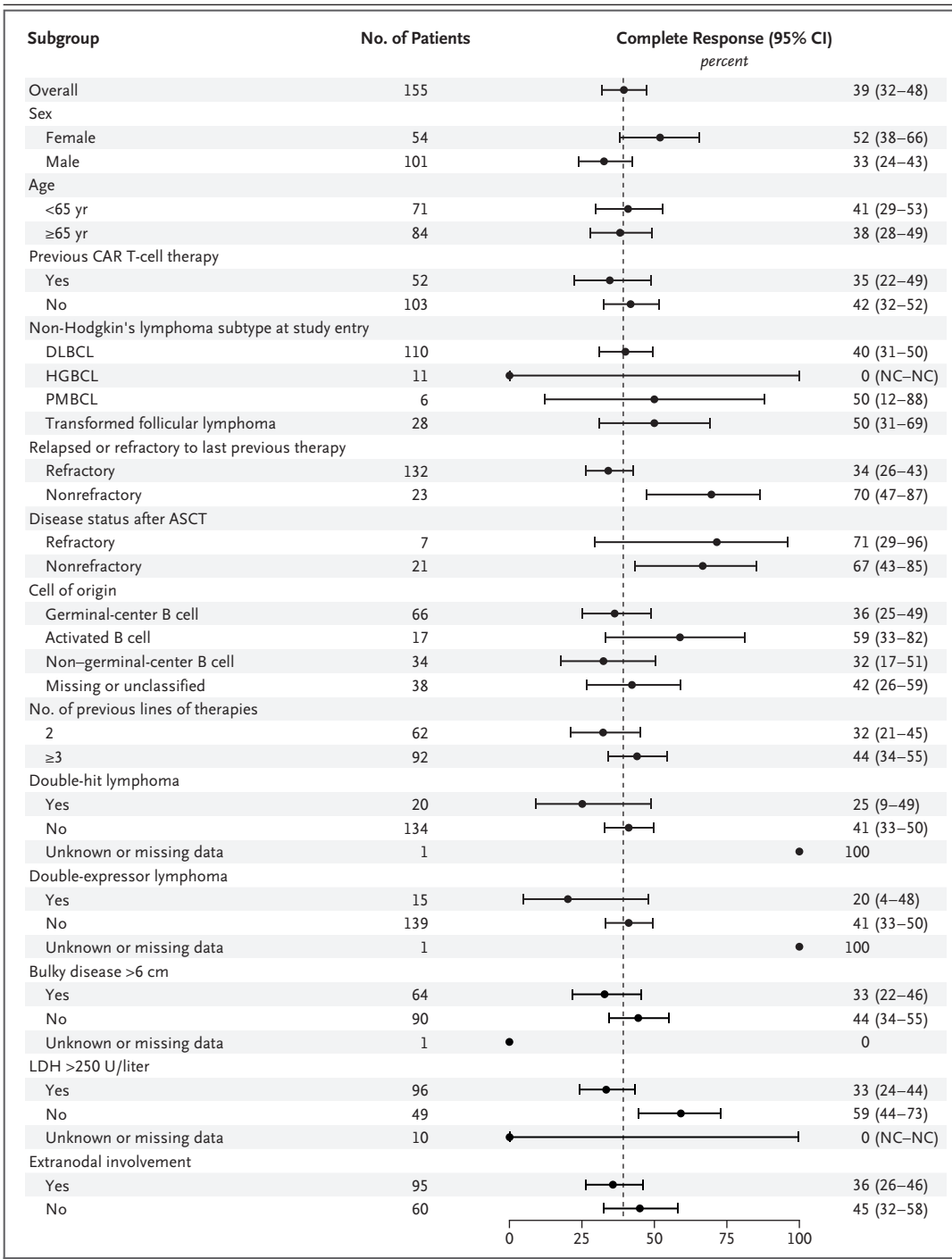
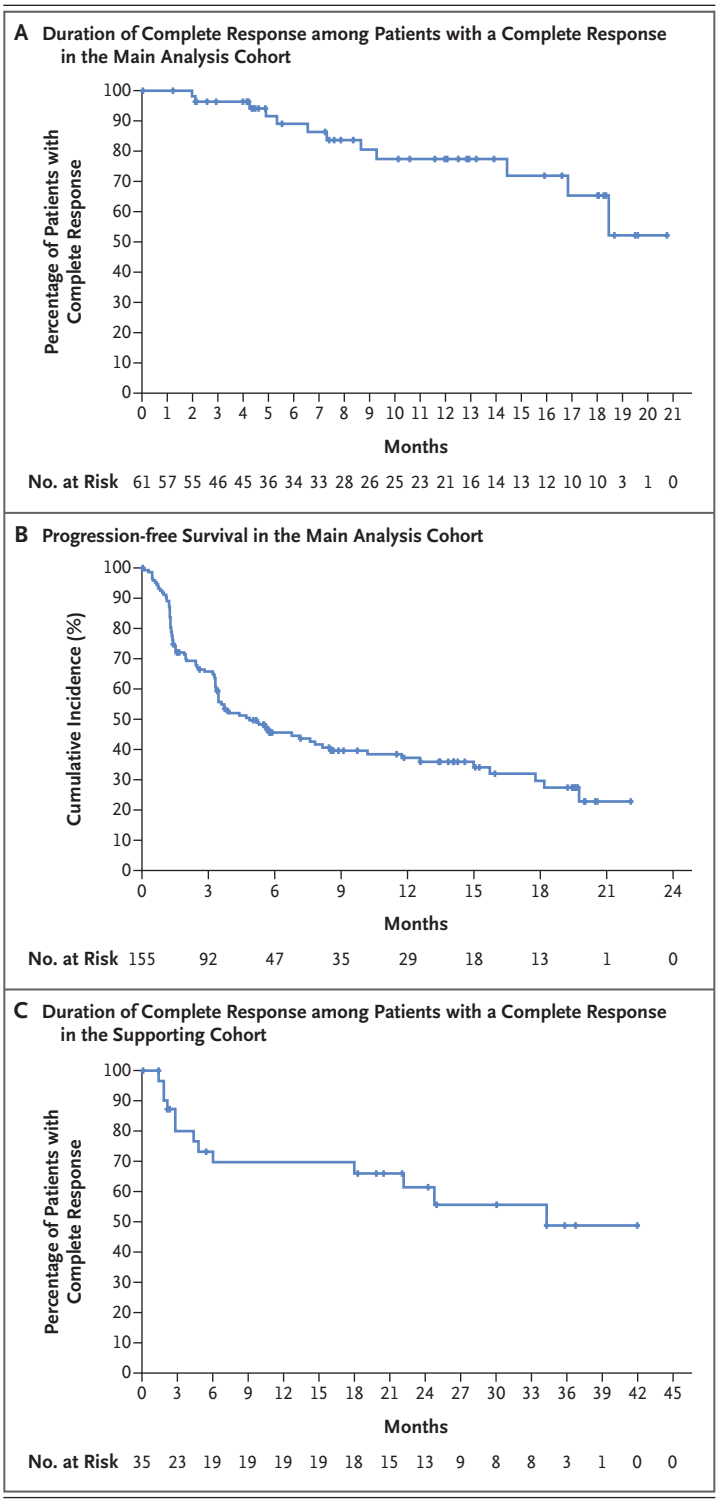


Figure 1. Prespecified Subgroup Analysis of Complete Response (Intention-to-Treat Population).

The intention-to-treat population included all the patients in the main analysis cohort. Complete response was determined by an independent review committee. The dashed line indicates complete response in the overall main analysis cohort. The confidence interval could not be calculated for three subgroups that included only one patient. In addition, the lower boundary of the confidence interval is not shown for two subgroups in which no patients had a complete response, given that the scale starts at 0. ASCT denotes autologous stem-cell transplantation, CAR chimeric antigen receptor, DLBCL diffuse large B-cell lymphoma, HGBCL high-grade B-cell lymphoma, LDH lactate dehydrogenase, NC not calculable, and PMBCL primary mediastinal large B-cell lymphoma.

Figure 2. Kaplan–Meier Plots of Complete Response and Progression-free Survival.

Complete response was determined by an independent review committee, both in the main analysis cohort (Panel A) and the supporting cohort (Panel C). The supporting cohort, which included patients who met the same inclusion and exclusion criteria as those in the main analysis cohort, included patients who had been treated in earlier cohorts with glofitamab doses of 10 mg or higher but lower than the phase 2 dose. Late events in the supporting cohort were progressive disease at 17.9 months, progressive disease at 22.1 months (patient received retreatment with glofitamab and was in remission as of the 24-month follow-up visit), death from unknown cause at 24.7 months, and death from acute myeloid leukemia at 34.2 months. In all panels, tick marks indicate censored data.



S6); these data included five deaths related to coronavirus disease 2019 (Covid-19). (Corresponding data for the pivotal cohort are shown in Fig. S7.) At the data-cutoff date, 87% of patients with a complete response (53 of 61) were alive, and 74% of the patients with an objective response (59 of 80) were alive.

In the supporting cohort, in which we explored the long-term outcomes in patients with a complete response, 35% of the patients (35 of 101) had a complete response. In this cohort, the median duration of complete response was 34.2 months (95% CI, 17.9 to not reached), with two relapses and two deaths occurring after 17 months (Fig. 2).

SAFETY

Adverse events leading to the discontinuation of treatment were uncommon, occurring in 14 of 154 patients (9%) (Table 3). Five patients (3%) had a glofitamab-related adverse event leading to treatment discontinuation (gastrointestinal hemorrhage in 1 patient, myelitis in 1, cytokine release syndrome in 1, and neutropenia in 2). Grade 3 or higher adverse events occurred in 62% of the patients. Grade 5 (fatal) adverse events (not including progressive disease) occurred in 8 patients (5%; Covid-19–related pneumonia or Covid-19 in 5, sepsis in 2, and delirium in 1) (Table 3). Patient narratives for the sepsis and delirium events are provided in the Supplementary Appendix; no deaths were considered by the investigators to be related to glofitamab therapy. The most common grade 3 or 4 adverse event was neutropenia (in 27% of the patients); this event did not lead to treatment discontinuation in most cases (Table 3 and Tables S4 and S5). (Corresponding data for the pivotal cohort are shown in Tables S6, S7, and S8.)

The most common adverse event was cytokine release syndrome (in 97 of 154 [63%] patients, as assessed according to the ASTCT criteria) (Table 3), which was primarily associated with the first three glofitamab doses (median time to onset from the cycle 1, day 8 dose, 13.5 hours [range, 6.0 to 52.0]; median duration, 30.5 hours [range, 0.5 to 317.0]); events were mostly of low grade according to the ASTCT criteria (grade 1 [fever] in 47% of the patients and grade 2 in 12%). High-grade cytokine release syndrome was uncommon (grade 3 in 3% of the patients and grade 4 in 1%) (Fig. S8). (Corresponding data for the pivotal cohort are shown in Fig. S9.) Further details, including an overview of the management of cytokine release syndrome, are provided in Tables S9 and S10, with corresponding data for the pivotal cohort shown in Table S11. One event of cytokine release syndrome led to the discontinuation of glofitamab. Seven patients with cytokine release syndrome were admitted to an intensive care unit. Of the 44 serious adverse events of cytokine release syndrome that were reported with glofitamab therapy, 43 were classified as serious owing to required or prolonged hospitalization. One event was unresolved (the patient died from progressive disease while the adverse event was ongoing). Premedication in the mandatory dexamethasone cohort led to a lower incidence of any-grade cytokine release syndrome than treatment with any glucocorticoid (48% vs. 68%). Cytokine release syndrome of grade 2 or higher (in 10% of patients) occurred just after the first infusion in this cohort; no events of cytokine release syndrome of grade 2 or higher were observed in patients after the second or subsequent doses of glofitamab (Fig. S10A).

CTCAE-defined neurologic adverse events consistent with ICANS occurred in 12 patients (8%), with events of grade 3 or higher in 3% (Table 3). These events were considered by the investigator to be related to glofitamab therapy in 3 patients (2%). All these events (dysphonia, confusional state, and disorientation, all of grade 1 or 2) resolved.

Infections were observed in 59 patients (38%), and 23 patients (15%) had infection of grade 3 or higher. The most frequent infections were Covid-19 or Covid-19–related pneumonia (in 14 patients [9%], with events of grade ≥3 in 9 [6%]) and sepsis (in 6 patients [4%], with all events being of grade ≥3). There were low incidences of febrile neutropenia (grade ≥3, in 4 patients [3%]), tumor lysis syndrome (grade ≥3, in 2 patients [1%]), and tumor flare (grade ≥2, in 11 patients [7%]) (Table 3).

DISCUSSION

In this study, glofitamab therapy led to a complete response in 39% of the patients with poor-prognosis DLBCL, in which treatment is often ineffective. Responses were observed early, usually at the first scheduled response assessment (at approximately 1.4 months). Responses were durable, with 78% of the patients with a complete response continuing to have remission at 12 months. The estimated 12-month overall survival of 50% was meaningful given the poor prognosis with conventional chemotherapy in this disease. Long-term follow-up data from the supporting cohort of patients who had a complete remission at lower doses of glofitamab confirm that durable complete remissions lasting several years can be observed with this fixed-duration treatment.

The population of our study reflects the current clinical landscape. Patients in our study were heavily pretreated and had disease that was highly refractory. Approximately one third of the patients had disease progression after the receipt of CAR T-cell therapy.

Cross-trial comparisons need to be interpreted with caution owing to differences in trial design and patient populations. Trials of CAR T-cell therapies have shown that 40 to 58% of patients who receive the infusion have a complete response.[17,18,29] In practice, rapidly progressing or debilitating disease can outpace manufacturing, which can preclude delivery of the autologous cellular product.

The percentage of patients with a complete response after glofitamab therapy compares well with those observed with other approved new options for the treatment of relapsed or refractory DLBCL, such as polatuzumab–bendamustine and rituximab (40% at end of treatment),[30] tafasitamab with lenalidomide (40%),[31] selinexor (12%),[15] and loncastuximab tesirine (24%).[11] As

Table 3. Adverse Events in All the Patients Treated at the Phase 2 Dose (Safety Population).*

Event	Patients (N = 154)
	no. (%)
Any adverse event	152 (99)
Most common adverse events	
Cytokine release syndrome, per ASTCT	97 (63)
Cytokine release syndrome, per Lee et al.[28]	101 (66)
Neutropenia	58 (38)
Anemia	47 (31)
Thrombocytopenia†	38 (25)
Any glofitamab-related adverse event	140 (91)
Any grade 3 or 4 adverse event	87 (56)
Most common grade 3 or 4 adverse events	
Neutropenia	41 (27)
Anemia	10 (6)
Thrombocytopenia	12 (8)
Any glofitamab-related grade 3 or 4 adverse event	64 (42)
Any serious adverse event	73 (47)
Most common serious adverse events‡	
Cytokine release syndrome, per ASTCT	32 (21)
Sepsis	6 (4)
Tumor flare	5 (3)
Covid-19–related pneumonia	5 (3)
Covid-19	4 (3)
Adverse events of special interest	
Cytokine release syndrome, grade ≥2 per ASTCT	24 (16)
Cytokine release syndrome, grade ≥2 per Lee et al.[28]	28 (18)
Infection, any grade	59 (38)
Neurologic event, grade ≥2	23 (15)
Event grade consistent with ICANS, any grade§	12 (8)
Tumor flare, grade ≥2	11 (7)
AST, ALT, or total bilirubin elevation, grade ≥2	11 (7)
Febrile neutropenia, grade ≥3	4 (3)
Tumor lysis syndrome, grade ≥3	2 (1)
Any grade 5 adverse event	8 (5)
Any glofitamab-related grade 5 adverse event	0
Any adverse event leading to discontinuation of glofitamab	14 (9)
Any glofitamab-related adverse event leading to discontinuation of glofitamab	5 (3)
Any adverse event leading to interruption in glofitamab treatment	28 (18)
Any glofitamab-related adverse event leading to interruption in glofitamab treatment	14 (9)

* Cytokine release syndrome was graded according to the approach of the American Society for Transplantation and Cellular Therapy (ASTCT) and the approach of Lee et al.[28] The most common adverse events were those that occurred in at least 20% of the patients, the most common grade 3 or 4 adverse events those that occurred in at least 5% of the patients, and the most common serious adverse events those that occurred in at least 2% of the patients. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and Covid-19 coronavirus disease 2019.

† The adverse event of thrombocytopenia included decrease in the platelet count.

‡ The most common serious adverse events listed were of any grade.

§ Events were described on the basis of Common Terminology Criteria for Adverse Events terms consistent with the immune effector cell–associated neurotoxicity syndrome (ICANS), as outlined by Lee et al.[28]

compared with other CD20×CD3 antibodies for DLBCL, glofitamab is unique owing to its fixed treatment duration and the relatively low number of visits to the treating center that are required over time. The percentage of patients with a complete remission (39%) is similar to reported data regarding the phase 2 dose of epcoritamab[32] and compares favorably with phase 1–2 data regarding odronextamab.[33] Both these bispecific antibodies are administered until disease progression; however, data from our study indicate that such an approach is not required with glofitamab in order for durable remission to occur.

Grade 3 or higher toxic effects after the receipt of glofitamab occurred in 62% of the patients and were predominantly hematologic. Cytokine release syndrome was the most frequent adverse event (in 63% of the patients), given that it is a common adverse event with T-cell–engaging immunotherapies. Mitigation strategies were implemented to reduce the incidence and severity of cytokine release syndrome. In our study, pretreatment with obinutuzumab to deplete peripheral B cells[23] and step-up doses of glofitamab enabled the use of an early high target dose of glofitamab (30 mg) while mitigating the severity of cytokine release syndrome. High-grade cytokine release syndrome was uncommon, and there were no grade 5 (fatal) events. Most events of cytokine release syndrome were associated with initial administration of glofitamab (in cycle 1), with a predictable time of onset. The symptoms could be controlled without the use of multiple pressors, with management relying mainly on glucocorticoids and tocilizumab. Only one patient discontinued treatment owing to cytokine release syndrome, and the incidence of symptoms of grade 3 or higher were lower with glofitamab (in 4% of patients) than with the CAR T-cell therapies axi-cel (in 11%,[34] with events graded according to the criteria of Lee et al.[27]) and tisa-cel (in 23%,[35], with events graded according to the Penn grading scale[36]). The incidence was similar to that observed with liso-cel (in 4.1% of patients,[37] with events graded according to the criteria of Lee et al.[27]). In the mandatory dexamethasone cohort, cytokine release syndrome of grade 2 or higher (in 4 of 40 patients [10%]) occurred just after the first infusion.

In contrast to CAR T-cell therapies, for which the incidence of neurologic adverse events of grade 3 or higher has been reported to be 32% with axi-cel,[36] 11% with tisa-cel,[37] and 12% with liso-cel,[37] the CTCAE-defined neurologic adverse events consistent with ICANS that were observed with glofitamab therapy were uncommon and mostly mild (grade ≥3 events in 3% of the patients). The incidence of treatment discontinuation due to adverse events was low. Most fatal adverse events (5 of 8 events) were related to Covid-19. The efficacy of glofitamab therapy, its novel mechanism of action, and unique 2:1 structure provide a strong rationale for combinations with other treatments.

In this phase 2 study involving patients with DLBCL, we found that a fixed course of glofitamab therapy induced durable complete responses and is a new active therapy for patients with this disease.

Supported by F. Hoffmann–La Roche.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families; the study coordinators and nurses and the representatives of the sponsor who were involved in data collection and analysis; and Louise Profit, Ph.D., of Ashfield MedComms, an Inizio company, for medical writing assistance with an earlier version of the manuscript.

APPENDIX

The authors' affiliations are as follows: the Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and the University of Melbourne, Melbourne, VIC (M.J.D.), and Prince of Wales Hospital and the University of New South Wales, Sydney (M. Hertzberg) — all in Australia; Humanitas University and Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) Humanitas Research Hospital (C.C.-S.), and Università degli Studi di Milano and Fondazione IRCCS Istituto Nazionale dei Tumori (P.C.) — all in Milan; Université de Lille, Centre Hospitalier Universitaire (CHU) Lille, Unité Labellisée de Recherche 7365, Groupe de Recherche sur les Formes Injectables et les Technologies Associées, Lille (F.M.), Centre Hospitalier Lyon Sud, Lyon (E.B.), and CHU de Montpellier, Centre National de la Recherche Scientifique, Unité Mixte de Recherche 5535, Montpellier (G.C.) — all in France; Vall d'Hebron University Hospital (G.I.) and Institut Català d'Oncologia Hospitalet, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Universitat de Barcelona (A.S.) — both in Barcelona; the Allegheny Health Network Cancer Institute, Pittsburgh (C.K.); Uniwersytet Medyczny we Wrocławiu, Wroclaw, Poland (T.W.); Universitair Ziekenhuis Gent, Ghent, Belgium (F.O.); the First Faculty of Medicine, Charles University Hospital, Prague, Czech Republic (M.T.); National Taiwan University Hospital, Taipei (S.-J.W.); F. Hoffmann–La Roche, Basel, Switzerland (D.P.-C., L.L.); Roche Products, Welwyn Garden City, United Kingdom (J.R., M.D., E.C., K.H.); and Rigshospitalet, Copenhagen (M. Hutchings).

REFERENCES

1. Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood 2015;125:22-32.
2. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184-90.
3. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130:1800-8.
4. van Imhoff GW, McMillan A, Matasar MJ, et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: the ORCHARRD study. J Clin Oncol 2017;35:544-51.
5. Bishop MR, Dickinson M, Purtill D, et al. Second-line tisagenlecleucel or standard care in aggressive B-cell lymphoma. N Engl J Med 2022;386:629-39.
6. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med 2022;386:640-54.
7. Ayers EC, Margolis D, Landsburg DJ. Real world outcomes in patients with relapsed/refractory diffuse large B-cell lymphoma receiving palliative intent therapies. Clin Lymphoma Myeloma Leuk 2020;20:661-7.
8. Chien H-C, Morreall D, Patil V, et al. Real-world practice patterns and outcomes in veterans with relapsed/refractory diffuse large B-cell lymphoma. Future Oncol 2021;17:411-22.
9. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the international CORAL study. Bone Marrow Transplant 2016;51:51-7.
10. Sehn LH, Salles G. Diffuse large B-cell lymphoma. N Engl J Med 2021;384:842-58.
11. Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol 2021;22:790-800.
12. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2020;38:155-65.
13. Salles G, Duell J, González Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. Lancet Oncol 2020;21:978-88.
14. Keating GM. Pixantrone: a review in relapsed or refractory aggressive non-Hodgkin's lymphoma. Drugs 2016;76:1579-86.
15. Kalakonda N, Maerevoet M, Cavallo F, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. Lancet Haematol 2020;7(7):e511-e522.
16. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377:2531-44.
17. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 2019;380:45-56.
18. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet 2020;396:839-52.
19. Guidetti A, Perrone G, Coluccia P, et al. The real life accessibility to CAR T-cell therapy: current experience in the only active center in Italy. 2019;134:Suppl 1:5619. abstract.
20. Jain MD, Jacobs MT, Nastoupil LJ, et al. Characteristics and outcomes of patients receiving bridging therapy while awaiting manufacture of standard of care axicabtagene ciloleucel CD19 chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory large B-cell lymphoma: results from the US Lymphoma CAR-T Consortium. Blood 2019;134:Suppl 1:245. abstract.
21. Kuhnl A, Roddie C, Tholouli E, et al. Real-world data of high-grade lymphoma patients treated with CD19 CAR-T in the UK. Br J Haematol 2020;189:30-1. abstract.
22. Roschewski M, Longo DL, Wilson WH. CAR T-cell therapy for large B-cell lymphoma — who, when, and how? N Engl J Med 2022;386:692-6.
23. Bacac M, Colombetti S, Herter S, et al. CD20-TCB with obinutuzumab pretreatment as next-generation treatment of hematologic malignancies. Clin Cancer Res 2018;24:4785-97.
24. Hutchings M, Morschhauser F, Iacoboni G, et al. Glofitamab, a novel, bivalent CD20-targeting T-cell-engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a phase I trial. J Clin Oncol 2021;39:1959-70.
25. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-68.
26. National Cancer Institute. Common terminology criteria for adverse events (CTCAE), v4.03. 2010 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).
27. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124:188-95.
28. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625-38.
29. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20:31-42.
30. European Medicines Agency. Polivy summary of product characteristics (https://www.ema.europa.eu/en/documents/product-information/polivy-epar-product-information_en.pdf).
31. European Medicines Agency. Minjuvi summary of product characteristics (https://www.ema.europa.eu/en/documents/product-information/minjuvi-epar-product-information_en.pdf).
32. Thieblemont C, Phillips T, Ghesquieres H, et al. Primary results of subcutaneous epcoritamab dose expansion in patients with relapsed or refractory large B-cell lymphoma: a phase 2 study. Presented at EHA2022, Vienna, June 9–12, 2022. LB2364. abstract.
33. Bannerji R, Arnason JE, Advani RH, et al. Odronextamab, a human CD20×CD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial. Lancet Haematol 2022;9(5):e327-e339.
34. European Medicines Agency. Yescarta summary of product characteristics (https://www.ema.europa.eu/en/documents/product-information/yescarta-epar-product-information_en.pdf).
35. European Medicines Agency. Kymriah summary of product characteristics (https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf).
36. Porter D, Frey N, Wood PA, Weng Y, Grupp SA. Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenlecleucel. J Hematol Oncol 2018;11:35.
37. Bristol Myers Squibb. Breyanzi highlights of prescribing information. June 2022 (https://packageinserts.bms.com/pi/pi_breyanzi.pdf).