Epcoritamab, lenalidomide, and rituximab versus lenalidomide and rituximab for relapsed or refractory follicular lymphoma (EPCORE FL-1): a global, open-label, randomised, phase 3 trial

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Summary

Background An unmet need persists for chemotherapy-free regimens that induce durable responses for relapsed or refractory follicular lymphoma. Lenalidomide and rituximab (R²) is an accepted standard of care in this population. The EPCORE FL-1 trial aimed to evaluate the efficacy and safety of epcoritamab plus R² versus R² in participants with relapsed or refractory follicular lymphoma after at least one previous line of chemoimmunotherapy.

Methods In this multicountry, open-label, phase 3 trial, participants were randomly allocated (1:1) to fixed-duration epcoritamab plus R² or R² for up to 12 cycles. Epcoritamab was administered weekly in cycles 1–3 and every 4 weeks in cycles 4–12, lenalidomide once daily during cycles 1–12 (days 1–21), and rituximab weekly during cycle 1 and monthly in cycles 2–5. The dual primary endpoints were overall response rate and progression-free survival by independent review committee. The data reported here are from a planned interim analysis carried out after 78% of progression-free survival events had occurred. This study is registered with ClinicalTrials.gov, NCT05409066, and EudraCT, 2021–000169–34, and is ongoing (closed to recruitment).

Findings Out of 668 participants screened for eligibility across 189 academic and non-academic centres in 30 countries across Africa, Asia, Australia, Europe, North America, and South America, a total of 488 participants were randomly allocated, 243 to epcoritamab plus R² and 245 to R². The trial met its dual primary endpoints, showing superiority of epcoritamab plus R² over R² in overall response rate and progression-free survival. With a median follow-up of 14·8 months (IQR 11·4–19·0), overall response rate was 95% (95% CI 92–97) with epcoritamab plus R² versus 79% (74–84; p<0·0001) with R². Progression-free survival was longer with epcoritamab plus R² versus R² (hazard ratio 0·21 [95% CI 0·14–0·31], p<0·0001); estimated 16-month progression-free survival favoured epcoritamab plus R² (85·5% *vs* 40·2%). Grade 3 or higher adverse events were more frequent with epcoritamab plus R² (219 [90%] of 243 participants) versus R² (161 [68%] of 238 participants). Cytokine release syndrome was low grade with epcoritamab plus R² (grade 1 in 28 [21%] participants and grade 2 in seven [5%] participants) and manageable, and all events were resolved.

Interpretation Epcoritamab plus R² resulted in significantly higher response rate and longer progression-free survival versus R² among participants with follicular lymphoma who had received at least one line of therapy. Epcoritamab plus R² had more grade 3 or higher adverse events versus R². Adverse events were manageable and consistent with the established safety profiles of the individual components, with no new safety findings identified. These findings position epcoritamab plus R² as a new standard of care for second-line or subsequent treatment of follicular lymphoma.

Funding AbbVie and Genmab.

Lancet 2026; 407: 161–73

Published Online December 7, 2025 https://doi.org/10.1016/S0140-6736(25)02360-8

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Introduction

Follicular lymphoma is the second most common B-cell non-Hodgkin lymphoma.[1] Although first-line chemoimmunotherapy provides patients with durable remission,[2,3] those with relapsed disease have shorter remission with each subsequent therapy.[4] The chemotherapy-free combination of lenalidomide plus rituximab (R²) is an internationally accepted standard in individuals with relapsed or refractory follicular lymphoma who have received at least one previous line of therapy (second-line or subsequent treatment of follicular lymphoma).[5–7] However, only about half of participants had a complete response with R² in clinical trials.[5,8] Similar response rates were observed in a

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Research in context

Evidence before this study

We searched PubMed and major international congresses from July 1, 2015, to July 17, 2025, for randomised clinical trials published in all languages that evaluated relapsed or refractory follicular lymphoma treatments using the search terms "follicular lymphoma" AND ("relapsed" OR "refractory") AND ("immunomodulatory" OR "lenalidomide"). From our searches, we found randomised phase 2 trials CALGB 50401 and HOVON110/Rebel and phase 3 trials AUGMENT, MAGNIFY, and inMIND. These studies supported the combination of lenalidomide and rituximab (R²) as an internationally accepted standard for individuals with relapsed or refractory follicular lymphoma. Although R² offers a therapeutic option, only around half of treated patients have a complete response and most relapse, needing subsequent treatments. The additions of bendamustine in the HOVON110/Rebel trial and tafasitamab in the inMIND trial improved efficacy outcomes with no unexpected toxicities. Early-phase trials are evaluating novel agents in combination with R² or immunomodulatory agent lenalidomide as chemotherapy-free options for follicular lymphoma after initial therapy. We hypothesised that the addition of epcoritamab with the R² regimen would enhance efficacy and minimise overlapping toxicities. In preclinical studies, epcoritamab worked well in the presence of rituximab, and lenalidomide enhanced activation of immune cells. In the phase 1b/2 EPCORE NHL-2 trial (NCT04663347), fixed-duration epcoritamab plus R² was evaluated in patients with relapsed or refractory follicular lymphoma, yielding deep and durable responses including an overall response rate of 96%, a complete response rate of 88%, and an estimated 24-month progression-free survival of 76%. On the basis of these results, the randomised, global, open-label, phase 3 EPCORE FL-1 trial (NCT05409066) was initiated to evaluate the efficacy and safety of epcoritamab plus R² versus R² alone in individuals with relapsed or refractory follicular lymphoma.

Added value of this study

This EPCORE FL-1 trial is, to our knowledge, the first phase 3 study of a bispecific antibody combination therapy in individuals with follicular lymphoma to be reported, and showed that the combination of epcoritamab plus R² significantly improved response rate and reduced the risk of disease progression or death compared with R². Benefit was observed across all explored participant subgroups, underscoring the generalisability of these results in the broader relapsed or refractory follicular lymphoma population. Although adverse events of grade 3 or higher were more frequent with the triplet versus R², these were manageable and consistent with the established safety profiles of the individual components of the triplet, with no new safety findings identified.

Implications of all the available evidence

In the landscape of studies in individuals with relapsed and refractory follicular lymphoma, epcoritamab and R² stands as the first bispecific-based, off-the-shelf, outpatient, fixed-duration, efficacious second-line or later therapy to represent a new and improved chemotherapy-free standard of care in this population. Additionally, this regimen could be a more accessible and convenient treatment option associated with longer remission.

single-centre real-world study,[9] underscoring the need for novel treatments that offer deeper and more durable responses and, consequently, improved long-term outcomes.

Epcoritamab is a subcutaneously administered bispecific antibody approved in numerous countries as monotherapy for follicular lymphoma after two or more lines of therapy.[10–14] Epcoritamab simultaneously binds the B-cell antigen CD20 and the T-cell antigen CD3, leading to T-cell-mediated cytotoxicity of CD20-expressing malignant B cells.[15–19] Rituximab induces complement-dependent cytotoxicity and natural killer cell-mediated antibody-dependent cellular cytotoxicity and macrophage phagocytosis.[16] Lenalidomide enhances proliferation and activation of both T cells and natural killer cells.[17] Unique among CD3×CD20 T-cell engagers, preclinical studies have found minimal interference between epcoritamab and rituximab antitumour activity when combined, because each targets a different epitope on CD20.[18] Furthermore, epcoritamab promotes natural killer cell activation and enhances rituximab-mediated cytotoxicity.[18,19] Collectively, these distinct and complementary modalities could augment antilymphoma activity and lead to improved clinical outcomes in individuals with relapsed or refractory follicular lymphoma.

Fixed-duration epcoritamab plus R² was evaluated in participants with relapsed or refractory follicular lymphoma in the phase 1b/2 EPCORE NHL-2 trial (NCT04663347). This triplet combination showed deep and durable responses (overall response rate 96%, complete response rate 88%, and estimated 24-month progression-free survival 76%).[14] On the basis of these encouraging results, the randomised phase 3 EPCORE FL-1 trial (NCT05409066, EudraCT 2021-000169-34)—comparing the efficacy and safety of epcoritamab plus R² versus R² alone in participants with relapsed or refractory follicular lymphoma after at least one previous line of chemoimmunotherapy—was initiated. Herein, we present the results of the main efficacy and safety analysis of this trial.

Methods

Study design and participants

This global, open-label, randomised phase 3 trial was carried out at 189 academic and non-academic centres in 30 countries across Africa, Asia, Australia, Europe, North

America, and South America (appendix pp 3–7). Participants aged 18 years and older who had histologically confirmed CD20-positive classic follicular lymphoma (formerly grade 1–3A follicular lymphoma) stage II, III, or IV, were relapsed or refractory after at least one previous antilymphoma regimen that contained an anti-CD20 monoclonal antibody with chemotherapy, had an Eastern Cooperative Oncology Group performance status of 0–2, met at least one Groupe d'Etude des Lymphomes Folliculaires (GELF) criterion, and had at least one site of measurable disease per Lugano criteria[20] were eligible (appendix pp 10–12). Demographic data on race, ethnicity, and biological sex at birth were self-reported. Changes to the protocol and major protocol deviations are in the appendix (pp 8–9).

The protocol (appendix pp 62–179) was approved by site-specific institutional review boards or independent ethics committees (appendix pp 31–61). The trial was carried out in accordance with the International Council for Harmonisation guidelines on Good Clinical Practice and the principles of the Declaration of Helsinki. All participants provided written informed consent. Participants were not involved in the design, conduct, or reporting of the trial.

Randomisation and masking

All participants were anonymised and assigned a unique identification number by the interactive response technology at the screening visit. Randomisation was stratified by region (USA and western Europe versus rest of the world) and by disease status and history: participants in second-line treatment were stratified by time from initiation of first-line therapy to disease progression (≤2 years *vs* >2 years), and participants in third-line or more treatment were stratified by time from end of last therapy to randomisation (<6 months *vs* ≥6 months). Region was chosen as a stratification factor because regional practice and reimbursement policies differ geographically and might affect access to and use of R². Disease status and history (progression of disease within 24 months, early relapse) were chosen as additional stratification factors as predictors of shorter survival and poor response to subsequent treatment. The study was open label with no masking to treatment.

Procedures

Participants were randomly allocated to receive epcoritamab plus R² (epcoritamab full dose 48 mg), epcoritamab plus R² (epcoritamab full dose 24 mg), or R² in 28-day cycles (appendix p 19). The 24 mg epcoritamab plus R² group was closed to enrolment based on the superior efficacy of the 48 mg dose shown in the EPCORE NHL-2 trial;[14] thus, only the 48 mg epcoritamab plus R² data are presented here. Participants in the 24 mg group were allowed to stay on treatment and follow-up. Fixed-duration epcoritamab was administered subcutaneously weekly during cycles 1–3, then every 4 weeks in cycles 4–12. The phase 3 epcoritamab schedule was selected to maximise response rates while preserving tolerability and convenience. Epcoritamab was administered on a step-up dosing (SUD) schedule during cycle 1 to mitigate the risk of cytokine release syndrome (CRS) using two SUD regimens—a two-SUD regimen (0·16 mg on cycle 1 day 1, 0·8 mg on cycle 1 day 8) or a three-SUD regimen (0·16 mg on cycle 1 day 1, 0·8 mg on cycle 1 day 8, 3 mg on cycle 1 day 15)—each followed by full doses of epcoritamab until completion, disease progression, unacceptable toxicity, or withdrawal of consent, whichever came first. The three-SUD regimen was implemented after reduced CRS severity and incidence had been observed in the EPCORE NHL-1 follicular lymphoma trial (NCT03625037).[21] CRS prophylaxis with dexamethasone was mandatory during the step-up doses in the first cycle. Details on protocol-specific CRS and antimicrobial prophylaxis are included in the appendix (pp 13–15). All participants received R², wherein lenalidomide was self-administered at the starting dose of 20 mg orally once a day from days 1–21 during cycles 1–12, and rituximab was administered intravenously at 375 mg per m² weekly during cycle 1 (days 1, 8, 15, and 22) and monthly during cycles 2–5 (on day 1).

See **Online** for appendix

Outcomes

This trial was designed to show the superiority of epcoritamab plus R² over R² with respect to overall response rate and progression-free survival. The primary comparison between the treatment groups was made in the intention-to-treat population, which includes all 488 randomly allocated participants.

The dual primary endpoints were overall response rate and progression-free survival assessed per the 2014 Lugano criteria[20] by an independent review committee. Disease assessment occurred starting at week 16 and continued per protocol or as clinically indicated. Key secondary endpoints were complete response rate per Lugano criteria assessed by an independent review committee, overall survival, and minimal residual disease negativity (appendix pp 17–18). Other prespecified secondary endpoints were changes from baseline in Functional Assessment of Cancer Therapy—Lymphoma (FACT-Lym), progression-free survival, best overall response, and complete response during the study, determined per Lugano criteria as assessed by investigator; and duration of response, duration of complete response, time to progression, complete response at the end of treatment (12 cycles), time to response, and time to complete response, determined per Lugano criteria as assessed by an independent review committee and by the investigator. Also included were time to next antilymphoma treatment and event-free survival, which was defined as the duration from randomisation to the date of any of the following (whichever occurred first): disease progression

determined by Lugano criteria as assessed by the investigator, initiation of any non-protocol-specified new antilymphoma therapy for any reason, or death. Changes from baseline in patient-reported outcome instruments (including Patient Global Impression of Severity, Patient Global Impression of Change, and EuroQol five-dimension, five-level questionnaire) were also prespecified secondary endpoints. These patient-reported outcome measures, complete response at the end of treatment (12 cycles), and minimal residual disease negativity were not available at the time of writing because longer-term follow-up is ongoing for these outcomes.

Statistical analysis

Up to the data cutoff date of May 24, 2025, there were two planned interim analyses for this study. The data reported herein were derived from the second planned interim analysis (488 participants) on May 24, 2025 (after 78% of the progression-free survival events had occurred). The first planned interim analysis on Jan 10, 2025, showed statistical significance on overall response rate, progression-free survival, and complete response rate,[22] and supported the US Food and Drug Administration approval[10,23] and additional submissions to other global health authorities for epcoritamab plus R² in relapsed or refractory follicular lymphoma. This first interim analysis—primarily focusing on overall response rate—occurred when the first 232 participants randomly allocated into the two treatment groups had at least 48 weeks of follow-up from the date of randomisation, and was calculated assuming 93% overall response rate for epcoritamab plus R² versus 75% overall response rate for R², with a power of 90% and a one-sided significance level of 0·005. For progression-free survival, the sample size was calculated assuming a hazard ratio (HR) of 0·6 (median progression-free survival of 65 months for epcoritamab plus R² *vs* 39 months for R²). A total of 181 progression-free survival events would provide at least 90% power and one-sided significance level of 0·025, when overall response rate is statistically significant. The study will continue to analyse long-term follow-up data for progression-free survival and preplanned key analysis for overall survival and minimal residual disease.

Overall response rate was analysed using the stratified Cochran–Mantel–Haenszel test. The Kaplan–Meier method was used to estimate the distribution of progression-free survival and the primary comparison between treatment groups used the stratified log-rank test. The estimate of the HR (epcoritamab plus R² *vs* R²) for the intention-to-treat population and the corresponding 95% CI were computed using a stratified Cox proportional hazards model with the treatment group as the only explanatory variable. Analysis of complete response rate followed the same methodology as overall response rate, and analyses of duration of response, duration of complete response, time to next antilymphoma treatment, and overall survival followed the same methodology as progression-free survival. On the basis of the median follow-up, supportive landmark estimates of progression-free survival, overall survival, and time to next antilymphoma treatment were derived from the respective Kaplan–Meier analyses. Prespecified subgroup analyses of primary and secondary endpoints were done according to baseline and disease characteristics.

This significance level was partitioned between the dual primary endpoints: 0·005 was allocated to the overall response rate (best overall response of complete response or partial response) analysis, and 0·02 was assigned to the progression-free survival analysis. To control the overall type I error rate, the efficacy endpoints were formally tested sequentially for each of the primary and key secondary endpoints in the following fixed sequence hierarchical order. The significance thresholds listed below for overall response rate, progression-free survival, and complete response rate were used at the first interim analysis and for overall survival at the second interim analysis.

Overall response rate was tested at a one-sided significance level of 0·005 and the significance was reached, leading to testing of progression-free survival at a one-sided significance level of 0·0023 (based on 54% information fraction). Following significance of progression-free survival, complete response rate was tested at a one-sided significance level of 0·025. Following significance of complete response rate, overall survival analysis was conducted at one-sided significance level of 0·000005 (based on 24% information fraction). Because significance of overall survival was not reached, the minimal residual disease endpoint was not tested. The safety analysis set consisted of the 481 participants who received at least one dose of the study drug. Adverse events were rated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Safety was evaluated by adverse events, physical examinations, vital signs, and clinical laboratory testing. All adverse events were reported from the time of study drug administration until 30 days after lenalidomide discontinuation, 60 days after epcoritamab or rituximab discontinuation (whichever was later), or until the participant started new antilymphoma therapy; whichever occurred first was collected. An independent data monitoring committee was in place to monitor safety data at a regular cadence. CRS and immune cell-associated neurotoxicity syndrome were graded according to the American Society for Transplantation and Cellular Therapy criteria.[24]

Participant-reported outcome analysis using linear mixed-effects models with repeated measures assessed change from baseline in FACT-Lym, which includes the FACT-Lym Lymphoma Subscale (LymS), trial outcome index (TOI), and total score. The lower bounds of minimally important difference thresholds for

	Epcoritamab plus R² (n=243)	R² (n=245)
Age		
Median, years	60 (50–69)	63 (54–71)
<65 years	155 (64%)	139 (57%)
≥65 years	88 (36%)	106 (43%)
Sex		
Male	139 (57%)	138 (56%)
Female	104 (43%)	107 (44%)
Region		
USA or western Europe	58 (24%)	60 (24%)
Rest of world	185 (76%)	185 (76%)
Race		
American Indian or Alaska Native	0	1 (<1%)
Asian	63 (26%)	54 (22%)
Black or African American	6 (2%)	2 (1%)
White	168 (69%)	184 (75%)
Multiple	1 (<1%)	1 (<1%)
Missing	5 (2%)	3 (1%)
Eastern Cooperative Oncology Group performance status		
0	166 (68%)	170 (69%)
1	72 (30%)	68 (28%)
2	5 (2%)	7 (3%)
FLIPI score at baseline		
0–1	63 (26%)	56 (23%)
2	79 (33%)	76 (31%)
3–5	100 (41%)	113 (46%)
Unknown	1 (<1%)	0
FLIPI-2 score at baseline		
0	23 (9%)	24 (10%)
1–2	144 (59%)	118 (48%)
3–5	51 (21%)	85 (35%)
Unknown	25 (10%)	18 (7%)
Follicular lymphoma grade		
1	61 (25%)	43 (18%)
2	126 (52%)	120 (49%)
3a	52 (21%)	75 (31%)
Classic, 5th edition WHO	3 (1%)	2 (1%)
Missing	1 (<1%)	5 (2%)
Ann Arbor stage		
II	37 (15%)	44 (18%)
III	74 (30%)	68 (28%)
IV	132 (54%)	133 (54%)
(Table 1 continues in next column)		

	Epcoritamab plus R² (n=243)	R² (n=245)
(Continued from previous column)		
Bulky disease (≥7 cm)		
Yes	47 (19%)	61 (25%)
No	191 (79%)	176 (72%)
Missing	5 (2%)	8 (3%)
Bone marrow involvement		
Positive	70 (29%)	68 (28%)
Negative	162 (67%)	168 (69%)
Unknown	11 (5%)	9 (4%)
Time from initial diagnosis to randomisation, years	4·5 (2·4–8·2)	5·3 (2·7–9)
Number of previous lines of antilymphoma therapy		
Median	1 (1–2)	1 (1–2)
1	145 (60%)	141 (58%)
2	58 (24%)	61 (25%)
≥3	40 (16%)	43 (18%)
Previous systemic therapies		
Any antilymphoma therapy	243 (100%)	245 (100%)
Anti-CD20 antibody	243 (100%)	245 (100%)
Anti-CD20 antibody with chemotherapy	239 (98%)	240 (98%)
Immunomodulatory	9 (4%)	13 (5%)
Refractory to previous therapy		
Refractory to first-line therapy	86 (35%)	81 (33%)
Progression of disease within 24 months*	106 (44%)	93 (38%)
Double refractory disease†	91 (37%)	91 (37%)
Refractory to previous anti-CD20 antibody	104 (43%)	103 (42%)
Refractory to last line of therapy	84 (35%)	82 (33%)

Data are median (IQR) or n (%). R²=lenalidomide plus rituximab. FLIPI=Follicular Lymphoma International Prognostic Index. *Defined as progression of disease 2 years or less from the date of initiation of first-line chemoimmunotherapy. †Double refractory is refractory to previous anti-CD20 antibodies and previous alkylating agents. Refractory is defined by either or both of: best overall response to treatment as stable disease or progressive disease, or progression occurring within 6 months after completion of treatment regardless of response.

Table 1: **Participant demographic and disease characteristics at baseline (intention-to-treat population)**

improvement or worsening were: LymS 2·9, TOI 5·5, and total score 6·5.[25]

Role of the funding source

Epcoritamab is being developed in collaboration between AbbVie (North Chicago, IL, USA) and Genmab (Copenhagen, Denmark), who funded this study and participated in the design of the study, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication.

Results

Between Sept 20, 2022, and Jan 10, 2025, 488 participants with relapsed or refractory follicular lymphoma were randomly allocated to receive epcoritamab plus R² (243 participants) or R² (245 participants). Demographics, baseline disease characteristics, and treatment history were generally balanced between groups (table 1). 213 (44%) participants had Follicular Lymphoma International Prognostic Index (FLIPI) score 3 or higher, 136 (28%) participants had FLIPI-2 score 3 or higher, and 108 (22%) participants had bulky masses (≥7 cm) at baseline. The majority, 286 (59%) participants, had received one previous line of therapy (median 1 [IQR 1–2]). Almost all participants (479 [98%]) had received an anti-CD20 antibody with chemotherapy; only

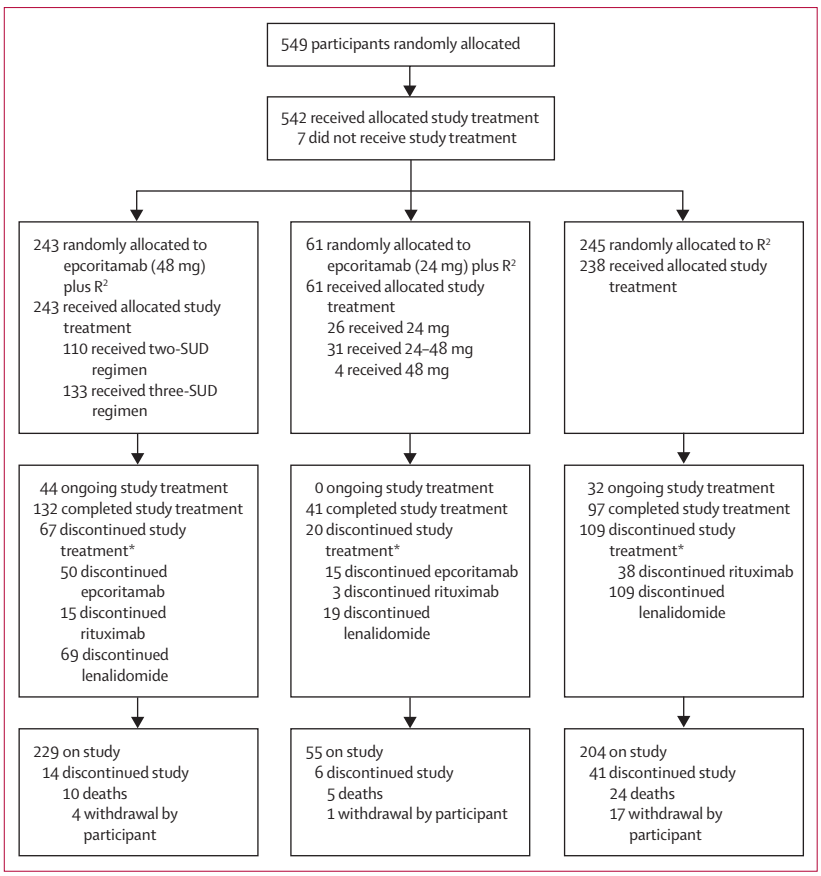


Figure 1: **Trial profile**
Participants were randomly allocated to receive epcoritamab plus R² (epcoritamab full dose 48 mg), epcoritamab plus R² (epcoritamab full dose 24 mg), or R² alone. The 24 mg epcoritamab plus R² group was closed to enrolment on the basis of the superior efficacy for the 48 mg dose that emerged in the EPCORE NHL-2 trial;[18] thus, only the 48 mg epcoritamab plus R² group and R² group data are presented here. R²=lenalidomide plus rituximab. SUD=step-up dosing. *Discontinued study treatment was defined as discontinuation of all study drugs, or discontinuation of one or more study drugs with the rest completed.

22 (5%) participants had received previous immunomodulatory agents (table 1). 182 (37%) participants were refractory to both anti-CD20 antibodies and alkylating agents, and 199 (41%) participants had progression of disease within 24 months of starting first-line chemoimmunotherapy.

At the time of the second interim analysis, 76 (16%) participants were continuing study treatment (44 [18%] of 243 participants receiving epcoritamab plus R² and 32 [13%] of 245 receiving R²). 229 (47%) participants (132 [54%] in the epcoritamab plus R² group and 97 [40%] in the R² group) completed treatment per protocol. 176 (36%) participants discontinued treatment, and seven (1%) never received the study treatment due to study withdrawal (figure 1, appendix p 24). Most participants were able to complete all planned epcoritamab doses, rituximab doses, and lenalidomide doses in both groups. Treatment exposures were similar between groups (appendix p 25).

The trial met its primary endpoints; both overall response rate and progression-free survival were significantly superior in the epcoritamab plus R² group compared with the R² group. As of the May 24, 2025, data cutoff, with a median follow-up of 14·8 months (IQR 11·4–19·0), data from efficacy endpoints, including overall response rate, are herein presented for all 488 randomly allocated participants in the epcoritamab plus R² and R² groups. Overall response rate was higher with epcoritamab plus R² (95% [95% CI 92–97]) than with R² (79% [74–84]), with a difference in overall response rate of 16% (10–22, p<0·0001; table 2). Complete response rate was 83% (77–87) in participants receiving epcoritamab plus R² compared with 50% (43–56) in the R² group, with a difference in complete response rate of 33% (25–41, p<0·0001). This complete response rate benefit was shown across all prespecified participant subgroups, including both low-risk and high-risk populations (appendix p 20). The median duration of response was not reached for epcoritamab plus R² and 11·5 months (95% CI 8·5–18·6) for R². The 12-month estimate of duration of response was 89·2% (95% CI 83·6–93·0) in the epcoritamab plus R² group versus 48·5% (38·8–57·5) in the R² group (table 2, appendix p 21). The median duration of complete response was not reached for epcoritamab plus R² and 18·6 months (11·1–not evaluable) for R²; the estimated 12-month duration of complete response was 91·2% (84·5–95·0) with epcoritamab plus R² versus 56·0% (42·4–67·6) with R² (table 2, appendix p 22). The median time to response and time to complete response were reached by the first disease assessment in both groups.

Epcoritamab plus R² led to longer progression-free survival compared with R² with 79% reduction in the risk of disease progression or death (HR 0·21 [95% CI 0·14–0·31], p<0·0001; table 2, figure 2A). Median progression-free survival was not reached in the epcoritamab plus R² group and was 11·7 months (95% CI 11·1–15·1) in the R² group. The estimated progression-free survival at 16 months, a timepoint chosen based on the duration of follow-up, was higher for epcoritamab plus R² (85·5%) than for R² (40·2%; table 2). This progression-free survival benefit was shown across all prespecified subgroups of participants (figure 2B). The results of the efficacy analysis were consistent between the investigator-assessed and the independent review committee-assessed endpoints (appendix p 26).

The median overall survival was not reached in either group (HR 0·38 [95% CI 0·18–0·80], p=0·0039; table 2) and 16-month overall survival rates were 95·8% for epcoritamab plus R² and 88·8% for R² (figure 3A). The estimated 16-month time to next antilymphoma treatment was 92·8% for epcoritamab plus R² and 64·9% for R² (HR 0·15 [0·09–0·27]; figure 3B).

In the safety population, which included 243 participants in the epcoritamab plus R² group and

238 participants in the R² group, more grade 3 or higher adverse and serious adverse events were observed in participants treated with epcoritamab plus R² than with R² (table 3). Grade 3 or higher neutropenia occurred in 167 (69%) of 243 participants receiving epcoritamab plus R² and 100 (42%) of 238 participants receiving R². Febrile neutropenia was observed in 15 (6%) participants receiving epcoritamab plus R² and six (3%) participants receiving R². Among participants who had neutropenia, 150 (83%) of 180 in the epcoritamab plus R² group and 75 (61%) of 123 in the R² group received granulocyte-colony stimulating factor. The median duration of neutropenia was 22 days in the epcoritamab plus R² group and 29 days in the R² group. Thrombocytopenia was observed in 67 (28%) of 243 participants receiving epcoritamab plus R² and 44 (18%) of 238 participants receiving R², and grade 3 or higher thrombocytopenia was observed in 23 (9%) participants receiving epcoritamab plus R² and 15 (6%) participants receiving R².

Any-grade infections were seen in 188 (77%) of 243 participants in the epcoritamab plus R² group and 125 (53%) of 238 in the R² group. The most common types of infections were COVID-19 (54 [22%] *vs* 32 [13%]), upper respiratory tract infection (49 [20%] *vs* 33 [14%]), and pneumonia (47 [19%] *vs* 20 [8%]). Grade 3 and 4 infections occurred in 81 (33%) participants receiving epcoritamab plus R² and 36 (15%) participants receiving R². Opportunistic infections occurred in 44 (18%) participants receiving epcoritamab plus R² and nine (4%) participants receiving R². The most common opportunistic infections were cytomegalovirus infection in 19 (8%) participants and herpes virus infection in 19 (8%) participants receiving epcoritamab plus R². *Pneumocystis jirovecii* pneumonia prophylaxis was administered over the course of treatment in 211 (87%) participants receiving epcoritamab plus R²; only one participant with *pneumocystis jirovecii* pneumonia infection was observed in this group. Herpes virus prophylaxis was administered in 172 (71%) participants receiving epcoritamab plus R². No fatal opportunistic infections were observed.

Among treated participants, ten (4%) deaths occurred in the epcoritamab plus R² group (four attributed to progressive disease; appendix p 27) compared with 23 (10%) in the R² group (11 attributed to progressive disease). Fatal adverse events were observed in four (2%) of 243 participants in the epcoritamab plus R² group and in nine (4%) of 238 participants in the R² group. Fatal infections were low in both groups and were not different between the two treatment groups. Cardiac failure due to multiorgan failure from sepsis and myocarditis concurrently with COVID-19 infection were observed in the epcoritamab plus R² group, and pneumonia, septic shock, and encephalitis in the R² group.

Treatment-emergent adverse events leading to treatment discontinuation occurred in 46 (19%) of 243 participants receiving epcoritamab plus R² and 29 (12%) of 238 participants receiving R² (table 3). Discontinuation of epcoritamab occurred in 21 (9%) participants, with infections being the most common cause (12 [5%]). Rituximab discontinuation occurred in seven (3%) participants from the epcoritamab plus R² group and 12 (5%) participants from the R² group. Lenalidomide discontinuation occurred in 45 (19%) participants receiving epcoritamab plus R² and 29 (12%) participants receiving R² (table 3); more participants discontinued due to infection, cytopenia, and rash in the epcoritamab plus R² group. Lenalidomide dose reduction was observed in 57 (23%) participants receiving epcoritamab plus R² and in 44 (18%) participants receiving R²; the most common causes were cytopenia and rash.

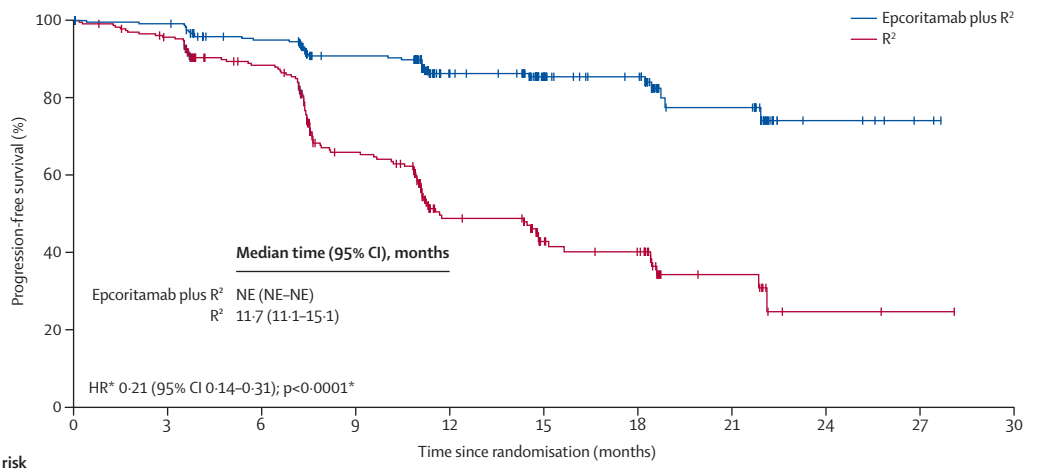
The incidence of CRS was lower for participants that received the three-SUD regimen compared with those who received the two-SUD regimen (35 [26%] of

	Epcoritamab plus R² (n=243)	R² (n=245)
Median follow-up, months, median (95% CI) [IQR]	14·8 (13·96–16·23) [12·0–19·3]	14·6 (13·57–15·64) [10·2–18·6]
Overall response rate, n (% [95% CI])*	231 (95% [92–97])	194 (79% [74–84])
Complete response, n (% [95% CI])*	201 (83% [77–87])	122 (50% [43–56])
Partial response	30 (12%)	72 (29%)
Stable disease	1 (<1%)	17 (7%)
Progressive disease	7 (3%)	16 (7%)
NE†	4 (2%)‡	18 (7%)‡
Duration of response		
Median, months§	NE (NE–NE)	11·5 (8·5–18·6)
12-month Kaplan–Meier estimate, %	89·2% (83·6–93·0)	48·5% (38·8–57·5)
Duration of complete response		
Median, months§	NE (NE–NE)	18·6 (11·1–NE)
12-month Kaplan–Meier estimate, %	91·2% (84·5–95·0)	56·0% (42·4–67·6)
Time to next antilymphoma treatment¶		
Median, months§	NE (NE–NE)	24·3 (18·2–NE)
16-month Kaplan–Meier estimate, %	92·8% (88·3–95·6)	64·9% (57·1–71·6)
Progression-free survival		
Median, months§	NE (NE–NE)	11·7 (11·1–15·1)
16-month Kaplan–Meier estimate, %	85·5% (79·7–89·7)	40·2% (31·8–48·4)
Time to progression		
Median, months§	NE (NE–NE)	14·8 (11·2–18·6)
Overall survival¶		
Median, months§	NE (NE–NE)	NE (NE–NE)
16-month Kaplan–Meier estimate, %	95·8% (92·0–97·8)	88·8% (83·6–92·4)
Event-free survival¶		
Median, months§	NE (NE–NE)	11·0 (9·1–12·5)

Data are n (%), median (95% CI), or Kaplan–Meier estimate % (95% CI) unless otherwise specified. R²=lenalidomide plus rituximab. NE=not evaluable. *95% CI is from the exact binomial distribution (Clopper–Pearson exact method). †Participants with no post-baseline disease assessment were also included. ‡NE: epcoritamab plus R² (n=4: 1 withdrawal, 2 deaths, 1 did not meet eligibility); R² (n=18: 8 withdrawals, 5 deaths, 3 did not meet eligibility, 1 clinical progression, 1 scan could not be read). §Based on Kaplan–Meier estimate. ¶Per investigator assessment.

Table 2: **Efficacy results according to independent review committee assessment (intention-to-treat population)**

A



Number at risk (censored)											
Epcoritamab plus R²	243 (0)	240 (1)	218 (13)	183 (39)	112 (102)	77 (136)	65 (148)	30 (179)	6 (202)	2 (206)	0 (208)
R²	245 (0)	220 (15)	180 (39)	110 (67)	58 (94)	34 (112)	28 (116)	10 (131)	2 (137)	1 (138)	0 (139)

B

	Epcoritamab plus R²		R²		HR (95% CI)
	Event/N (%)	Median, months	Event/N (%)	Median, months	Epcoritamab plus R² *vs* R²
All participants	35/243 (14·4)	NE (NE–NE)	106/245 (43·3)	11·7 (11·1–15·1)	0·22 (0·15–0·32)
Age, years					
<65	21/155 (13·5)	NE (NE–NE)	58/139 (41·7)	11·3 (10·9–18·6)	0·20 (0·12–0·33)
≥65	14/88 (15·9)	NE (18·9–NE)	48/106 (45·3)	14·5 (7·9–18·4)	0·24 (0·13–0·44)
<75	32/223 (14·3)	NE (NE–NE)	91/210 (43·3)	11·3 (11·0–15·6)	0·21 (0·14–0·32)
≥75	3/20 (15·0)	NE (NE–NE)	15/35 (42·9)	14·5 (7·5–NE)	0·26 (0·08–0·92)
Sex					
Male	23/139 (16·5)	NE (NE–NE)	54/138 (39·1)	14·5 (11·1–21·8)	0·25 (0·15–0·42)
Female	12/104 (11·5)	NE (NE–NE)	52/107 (48·6)	11·3 (9·7–15·1)	0·17 (0·09–0·31)
Region					
USA or western Europe	5/58 (8·6)	NE (NE–NE)	18/60 (30·0)	NE (11·1–NE)	0·18 (0·07–0·49)
Rest of world	30/185 (16·2)	NE (NE–NE)	88/185 (47·6)	11·2 (10·9–14·8)	0·22 (0·15–0·34)
Ann Arbor stage					
II	4/37 (10·8)	NE (NE–NE)	21/44 (47·7)	11·2 (9·6–NE)	0·16 (0·06–0·49)
III and IV	31/206 (15·0)	NE (NE–NE)	85/201 (42·3)	11·7 (11·0–18·4)	0·23 (0·15–0·35)
FLIPI score at baseline					
0–1	6/63 (9·5)	NE (NE–NE)	19/56 (33·9)	NE (11·1–NE)	0·18 (0·07–0·46)
2	8/79 (10·1)	NE (18·9–NE)	30/76 (39·5)	15·1 (11·2–21·8)	0·18 (0·08–0·40)
3–5	21/100 (21·0)	NE (21·9–NE)	57/113 (50·4)	10·8 (7·6–14·4)	0·25 (0·15–0·42)
Number of previous antilymphoma therapies					
1	20/145 (13·8)	NE (NE–NE)	58/141 (41·1)	14·4 (10·9–18·4)	0·20 (0·12–0·34)
2	9/58 (15·5)	NE (NE–NE)	26/61 (42·6)	11·1 (8·1–NE)	0·24 (0·11–0·52)
≥3	6/40 (15·0)	NE (NE–NE)	22/43 (51·2)	11·5 (8·2–NE)	0·23 (0·09–0·56)
Bulky disease per independent review committee (nodal or extranodal ≥7 cm)					
Yes	6/47 (12·8)	NE (NE–NE)	31/61 (50·8)	7·6 (7·4–11·2)	0·12 (0·05–0·28)
No	28/191 (14·7)	NE (NE–NE)	71/176 (40·3)	14·8 (11·2–21·8)	0·26 (0·17–0·41)
Progression of disease within 24 months					
Yes	22/106 (20·8)	NE (21·9–NE)	47/93 (50·5)	9·6 (7·5–11·2)	0·22 (0·13–0·37)
No	12/131 (9·2)	NE (NE–NE)	54/144 (37·5)	18·4 (11·7–22·1)	0·17 (0·09–0·32)
Double refractory					
Yes	19/91 (20·9)	21·9 (21·9–NE)	47/91 (51·6)	10·9 (7·5–11·3)	0·23 (0·13–0·39)
No	16/152 (10·5)	NE (NE–NE)	59/154 (38·3)	15·1 (11·7–NE)	0·19 (0·11–0·34)

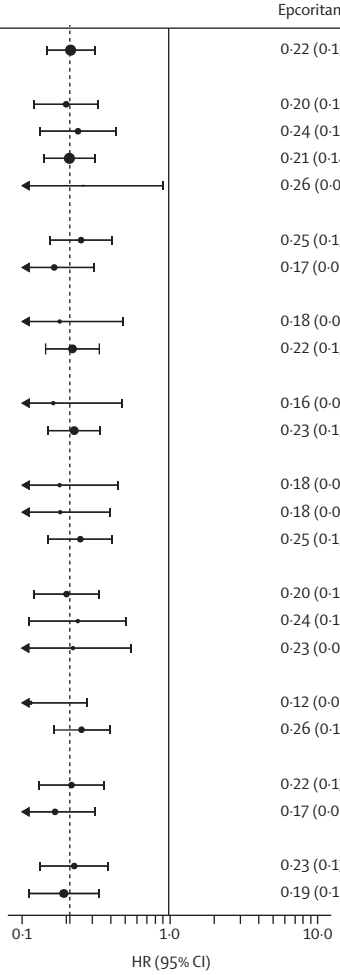


Figure 2: **Progression-free survival per independent review committee assessment in (A) the intention-to-treat population and (B) participant subgroups**
In (A), the tick marks indicate censored data. The p value is based on log-rank test. The HR is estimated using the Cox proportional hazards model. In (B), N represents the total number of participants within each category in each group. Arrows indicate that the CI is extended more than the current range. FLIPI=Follicular Lymphoma International Prognostic Index. HR=hazard ratio. NE=not evaluable. R²=lenalidomide plus rituximab. *Stratified by disease status and history.

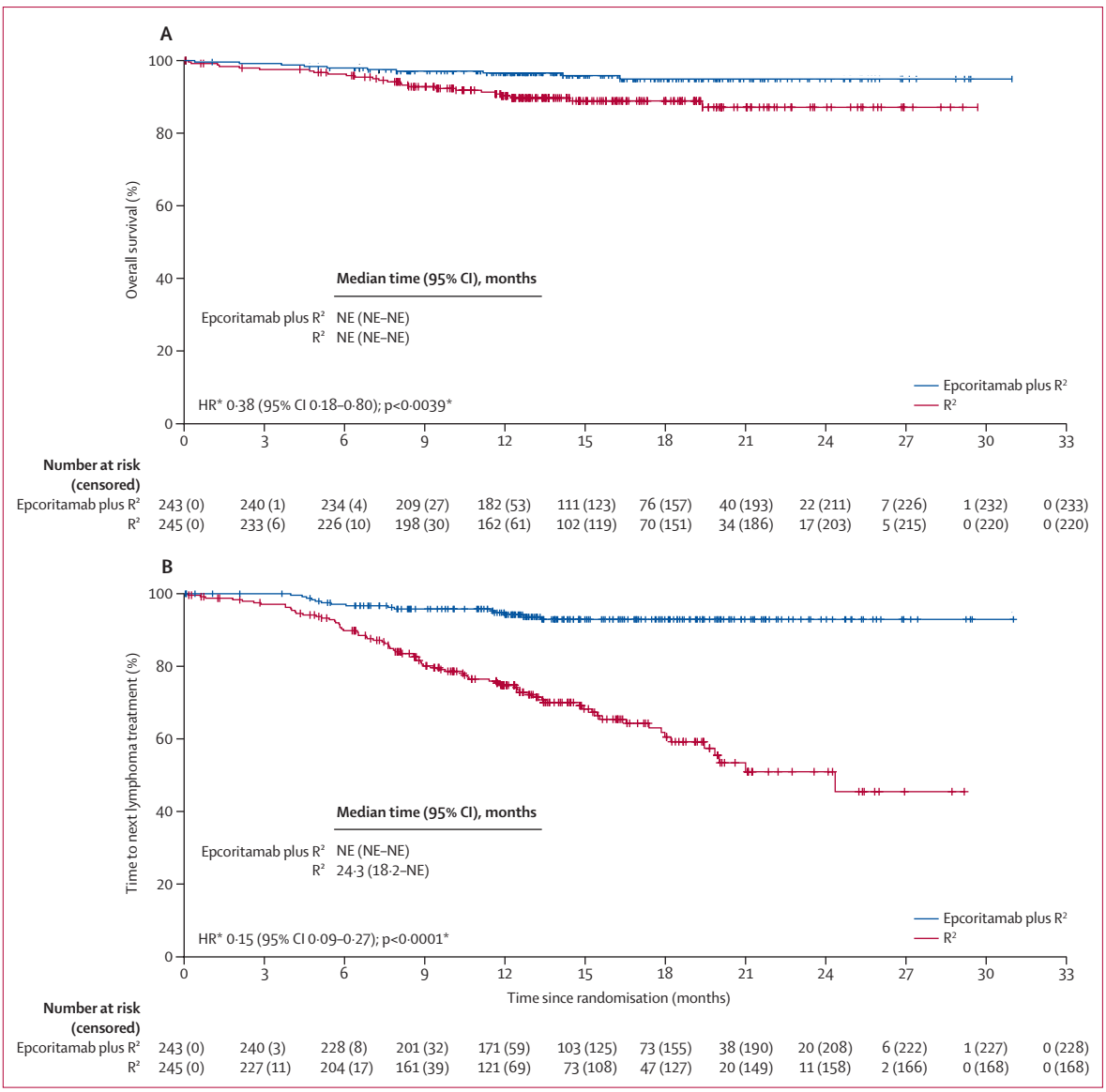


Figure 3: **Overall survival (A) and time to next lymphoma treatment per investigator assessment (B)**
Tick marks indicate censored data. The p value is based on log-rank test. The HR is estimated using the Cox proportional hazards model. HR=hazard ratio. NE=not evaluable. R²=lenalidomide plus rituximab. *Stratified by disease status and history.

133 *vs* 50 [45%] of 110 participants; appendix p 28). Among the 133 participants who received the three-SUD regimen, 35 (26%) experienced CRS, all of which were low grade (28 [21%] grade 1 and seven [5%] grade 2), and most events occurred after the first full dose (appendix p 28). The median time to CRS onset after the first full dose was 34·9 h (IQR 20·2–100·1), and the median time to resolution was 24·0 h (IQR 11·3–72·0). Tocilizumab was used in nine (26%) of the 35 participants who had CRS. Immune cell-associated neurotoxicity syndrome was reported in one participant in the epcoritamab plus R² group, which was grade 1 and resolved in 3 days. No clinical tumour lysis syndrome was reported in the study.

Participants had FACT-Lym quality of life baseline scores in the top 75% of the score range (appendix p 29). The mean changes from baseline for FACT-Lym scores were within the minimally important difference thresholds throughout treatment for each group, indicating that quality of life was preserved (appendix p 23). More specifically, while on treatment with epcoritamab plus R², FACT-Lym LymS, TOI, and total scores were maintained with least-squares mean changes of 1·55 (SE 0·546) for LymS, 0·39 (1·062) for TOI, and –0·11 (1·439) for total score at cycle 12 day 1. Similarly, in participants treated with R² alone, least-squares mean changes were 1·26 (0·591) for LymS, 0·75 (1·145) for TOI, and 0·33 (1·541) for total score at

	Epcoritamab plus R² (n=243)		R² (n=238)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	242 (>99%)	219 (90%)	235 (99%)	161 (68%)
Adverse event related to study drug	236 (97%)	203 (84%)	213 (90%)	129 (54%)
Serious adverse event	135 (56%)	..	69 (29%)	..
Adverse event leading to treatment discontinuation	46 (19%)	..	29 (12%)	..
Epcoritamab	21 (9%)	..	..	..
Rituximab	7 (3%)	..	12 (5%)	..
Lenalidomide	45 (19%)	..	29 (12%)	..
Adverse event of special interest ≥20%				
Infections*	188 (77%)	81 (33%)	125 (53%)	37 (16%)
Neutropenia	180 (74%)	167 (69%)	123 (52%)	100 (42%)
Cytokine release syndrome	85 (35%)	0	1 (<1%)	0
Anaemia	68 (28%)	19 (8%)	41 (17%)	11 (5%)
Thrombocytopenia	67 (28%)	23 (9%)	44 (18%)	15 (6%)
Pyrexia	58 (24%)	1 (<1%)	33 (14%)	3 (1%)
Rash	58 (24%)	19 (8%)	53 (22%)	9 (4%)
COVID-19	54 (22%)	7 (3%)	32 (13%)	4 (2%)

Data are n (%). The safety population consisted of all participants who received at least one dose of the study drug.
*Events were in the MedDRA system organ class "Infections and Infestations".

Table 3: **Adverse events and selected events of clinical interest (safety population)**

cycle 12 day 1. Comparatively, the mean difference of epcoritamab plus R² versus R² at the end of the treatment regimen (C12D1) for FACT-Lym LymS was 0·29 (95% CI –1·15 to 1·74), that for FACT-Lym TOI was –0·37 (–3·16 to 2·43), and that for FACT-Lym total score was –0·44 (–4·21 to 3·33).

Discussion

EPCORE FL-1 is, to our knowledge, the first phase 3 study of a bispecific antibody combination therapy in participants with relapsed or refractory follicular lymphoma to be reported and found that the combination of epcoritamab plus R² resulted in a deep and durable complete response rate of 83% and reduced the risk of disease progression or death by 79% compared with R². Participants with epcoritamab plus R² had longer time to next antilymphoma treatment compared with R². Although survival follow-up was short, deaths due to disease were lower in the epcoritamab plus R² group. Benefit was observed across all explored prespecified participant subgroups, underscoring the generalisability of these results in the broader relapsed or refractory follicular lymphoma population.

Ongoing phase 3 trials are also evaluating combinations with R², including tafasitamab in inMIND and tazemetostat in SYMPHONY-1, in relapsed or refractory follicular lymphoma. In the recently reported phase 3 inMIND trial, tafasitamab plus R² led to a 57% reduction in the risk of disease progression or death, 84% overall response rate, 45% complete response rate, and minimal overlapping toxicities to R².[26] These results led to the approval of tafasitamab in combination with R² in participants with relapsed or refractory follicular lymphoma.[27] The phase 1b/3 SYMPHONY-1 trial reported results from the phase 1b single-arm dose-finding portion of the study, with 91% overall response rate, 55% complete response rate, 18-month progression-free survival of 94% in the recommended 800 mg dose combined with R² cohort, and no new safety signal.[28] Phase 3 trials with CD3×CD20 bispecific in combination with lenalidomide (CELESTIMO and OLYMPIA-5) have yet to report results, but early-phase trials consistently reported complete response rates of more than 65%.[29–33]

The R² group median progression-free survival in this trial (11·7 months) and the inMIND trial (16·0 months[26]), were shorter compared with the AUGMENT trial (39·4 months[5]). Notably, participants with rituximab refractory follicular lymphoma were excluded from AUGMENT, whereas a substantial proportion of participants with anti-CD20 antibody refractory follicular lymphoma were included in both our trial and the inMIND trial (approximately 40% each). Furthermore, to be eligible for AUGMENT, participants were not required to meet GELF treatment criteria (only 97 [54%] of 178 participants did), whereas participants enrolled in our trial were all in need of therapy according to GELF criteria. Overall, both our trial and the inMIND trial reflected a higher-risk population, thereby accounting for the shorter progression-free survival on R² compared with AUGMENT. Comparing the populations between our trial and inMIND, the baseline demographic and disease characteristics, including Ann Arbor stage, follicular lymphoma grade, FLIPI, and proportion of refractoriness to previous therapy were similar; however, a key difference is that in our trial all participants had progressed after receiving an immunochemotherapy combination (ie, both anti-CD20 immunotherapy and alkylator-containing chemotherapy), which might represent a more treatment-resistant population than inMIND, where 7% of participants were treated with only anti-CD20 monotherapy.[26] Altogether, these distinctions might have contributed to a difference in progression-free survival for the control group between our trial and the inMIND trial.

The addition of epcoritamab to R² provided superior efficacy, albeit with a higher incidence of adverse events compared with R² alone. This finding underscores the need to balance the benefits against potential risks as well as optimised adverse event management. Infections and neutropenia were the most common adverse events, and were higher for participants treated with epcoritamab plus R² due to overlapping toxicities in line with previous reports of T-cell engaging immunotherapies.[14,26,29] Given the observed rates of grade 3 or higher infections in participants treated with epcoritamab plus R² versus R², attention should be given to antimicrobial prophylaxis and proactive monitoring. The three-SUD regimen substantially reduced the incidence and severity of CRS as all events

were low grade and reversible, and none led to treatment discontinuation. Adverse events were manageable and consistent with the established safety profiles of the individual components of the triplet,[5,13,18] with no new safety findings. Taken together, despite the higher incidence of adverse events with the addition of epcoritamab to R², participants experienced significantly higher progression-free survival and preserved their high baseline quality of life, which shows an overall favourable benefit–risk profile.

This study had limitations. First, an open-label design allows investigators to differentiate and manage CRS, but it informs participants and study investigators of treatment assignment. This study used independent review committee assessment of its dual primary endpoints to offset potential biases. Additionally, the study remained masked to the study team until efficacy at progression-free survival 75% information fraction was declared to maintain study integrity. Another limitation is the relatively short study median follow-up of 14·8 months. However, our data suggests a positive trend and an early potential survival benefit with epcoritamab plus R². More deaths were observed in the R² group compared with the epcoritamab plus R² group within the first 3 months, with the majority of deaths attributed to deterioration due to disease progression. A final analysis with longer follow-up for this study is planned and could shed light on comparative overall survival outcomes and provide additional information on potential long-term toxicities, including infections as a function of B-cell recovery over time. Additionally, baseline characteristics were generally balanced across the two treatment groups, except for a slightly higher proportion of participants aged 65 years or older, with FLIPI-2 scores 3–5, and with follicular lymphoma grade 3A in the R² group, because these were not controlled by stratification factors. Benefit was observed across all explored prespecified participant subgroups, underscoring the generalisability of these results in the broader relapsed or refractory follicular lymphoma population. Finally, although benefit was shown across all prespecified subgroups, there were limitations due to sample size in the assessment of previous bendamustine use on response. Bendamustine has previously been shown to result in T-cell exhaustion and lower response to T-cell dependent immunotherapy.[34] Here, the sample of participants with recent bendamustine use within 12 months was too small (seven participants) to provide meaningful conclusions.

In summary, in this phase 3 trial of participants with follicular lymphoma and at least one previous line of therapy, the primary analysis showed that fixed-duration epcoritamab plus R² was superior to standard-of-care R² with high complete response rates and substantial risk reduction of disease progression or death with a manageable safety profile in the outpatient setting. In the new era of chemotherapy-free options providing longer remission and potential cure, epcoritamab plus R² is positioned to replace R² as the new standard of care for second-line or subsequent treatment of follicular lymphoma.

Contributors

GS, JPM, NM, FZ, AA, and EF carried out the literature search. LF, MN, HH, KML, JFS, RT, MK, AC, TPV, RG, AJ-U, SAG, OB, CT, AT, AE-C, AI, JN, MAP, AM, DHY, DM, and FM enrolled participants and were study investigators. GS, JPM, NM, FZ, AA, and EF collected and assembled the data. LF, GS, JPM, NM, FZ, AA, and EF verified the data. All authors designed the study, had full access to and analysed the data, were involved in writing, reviewing, and editing the original and subsequent drafts of the published work, and were responsible for the final decision to submit for publication.

Declaration of interests

LF reports research funding from Roche, Genentech, Genmab, AbbVie, Innate Pharma, BeOne, and AstraZeneca; a grant paid to institution from Blood Cancer United (formerly the Leukemia & Lymphoma Society) and through the National Institutes of Health–National Cancer Institute Cancer Center Support Grant P30 CA008748; consultancy fees from Roche, Genentech, Genmab, AbbVie, Sanofi, AstraZeneca, and Merck; serving in an advisory role for AbbVie, Genentech, ADC Therapeutics, Seagen, Ipsen, Johnson & Johnson, and Regeneron; and honoraria from Roche, Genmab, AbbVie, and Kite. MN reports institutional research funding from Takeda; and consulting fees paid to institution from AbbVie. KML reports serving in a consultancy role for Kite, Gilead, Genmab, Roche, AbbVie, BeiGene, Bristol Myers Squibb, and Celgene; research funding from Kite–Gilead, Genmab, Roche, AbbVie, BeiGene, Bristol Myers Squibb, ADC Therapeutics, AstraZeneca, CellCentric, Janssen, MorphoSys, MSD, Nurix, Regeneron, Step Pharma, Viracta, Celgene, and the National Institute for Health and Care Research Manchester Biomedical Research Centre (NIHR203308); participation on speakers bureaus for AbbVie, Bristol Myers Squibb, and Celgene; travel support from Bristol Myers Squibb and Celgene; and serving as a member of the Epcoritamab Global Council. JFS reports serving in a consultancy role for TG Therapeutics and Bristol Myers Squibb; research funding from AbbVie, Bristol Myers Squibb, Janssen, Loxo, and Roche; and honoraria from AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Gilead, Janssen, Loxo, and Roche. RT reports serving in a consultancy role for AbbVie. AC reports honoraria from J&J, AbbVie, AstraZeneca, Lilly, Knight, BeiGene, Regeneron, Ipsen, and Pfizer; and research funding from AbbVie. TPV reports research support and being a principal investigator for Merck, Roche, AbbVie, Bristol Myers Squibb, and Karyopharm; honoraria from Takeda, Roche, Genesis Pharma, AbbVie, Gilead, Sandoz, AstraZeneca, Lilly, Janssen, Sobi, and Swixx; and serving in an advisory role for Roche, Genesis Pharma, Takeda, AbbVie, Merck, Gilead, Sandoz, Teva, AstraZeneca, Winmedica, Sobi, Swixx, and Lilly. RG reports research grants from Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, Bristol Myers Squibb, MSD, Sandoz, AbbVie, Gilead, and Daiichi Sankyo; consulting fees or other remuneration from Celgene, Novartis, Roche, Bristol Myers Squibb, Takeda, AbbVie, AstraZeneca, Janssen, MSD, Amgen, Merck, Gilead, Daiichi Sankyo, and Sanofi; holding stock in Novo Nordisk and Lilly; and support for attending meetings or travel from Lilly, Novo Nordisk, Roche, Amgen, Janssen, AstraZeneca, Novartis, MSD, Celgene, Gilead, Bristol Myers Squibb, and AbbVie. AJ-U reports consultancy or advisory roles for Regeneron, Kite–Gilead, Lilly, AbbVie, AstraZeneca, and Incyte; serving on speakers bureaus for Janssen, Sandoz, Roche, Incyte, Kite–Gilead, and AbbVie; and serving on advisory boards for AbbVie, AstraZeneca, Kite–Gilead, Incyte, Lilly, and Regeneron. OB reports serving in a consulting role for AbbVie, Janssen, Roche, AstraZeneca, and Lilly; research funding and speaker fees from AbbVie; and serving in an advisory role for Lilly and AbbVie. CT reports honoraria from ADC Therapeutics, AstraZeneca, Incyte, Sanofi, Amgen, Novartis, Cellectis, Janssen, Bayer, Roche, BeiGene, AbbVie, Bristol Myers Squibb–Celgene, Takeda, Kite–Gilead, and Regeneron; serving in a consultancy role for Novartis, Janssen, BeiGene, AbbVie, Bristol Myers Squibb–Celgene, Takeda, Kite–Gilead, and Regeneron; research funding from Roche, AbbVie, and Kite–Gilead; and previous employment by the

University of Paris. AT reports honoraria from Takeda, Regeneron, Novartis, AbbVie, Kite–Gilead, Incyte, AstraZeneca, Lilly, Kiowa Kyrin, and BeiGene. AE-C reports serving in an advisory role and receiving speaker fees from AbbVie and Janssen; and travel support from Roche. AI reports serving in a consultancy role for AbbVie, Bristol Myers Squibb, and Novartis; and honoraria from AstraZeneca and Takeda. MAP reports participation on an advisory board, serving in an advisory role, and serving as a speaker for Janssen, AbbVie, and AstraZeneca; and travel grants from Sanofi, Amgen, and Roche. AM reports research funding from AbbVie, Roche, MSD, and BeOne; and honoraria from BeOne, Biomab Innovation, and Roche. DHY reports serving in a consultancy role for AbbVie, AbClon, BeOne, Bristol Myers Squib, GI Cell, GC Cell, Verismo, J&J, Novartis, Regeneron, and Roche; patents and royalties from Boryung; research funding from AbbVie, BeOne, Boryung, Celltrion, Kyowa Kirin, Janssen, and Samyang; and honoraria from AbbVie, Bristol Myers Squib, Boryung, GSK, Kyowa Kirin, Novartis, Roche, Takeda, and J&J. DM reports serving in a consultancy role for Janssen, AstraZeneca, Chugai, AbbVie, Genmab, Sanofi, Bristol Myers Squib, Novartis, and Pfizer; research funding from Ono, Janssen, Eisai, Chugai, Kyowa Kirin, MSD, Samyang, Sanofi, Symbio, Takeda, AbbVie, AstraZeneca, Bristol Myers Squib, Novartis, Otsuka, Pfizer, Loxo Oncology, Eli Lilly, and Incyte Japan; and honoraria from Ono, Nippon Shinyaku, Janssen, Eisai, Chugai, Kyowa Kirin, MSD, Sanofi, Symbio, Takeda, AbbVie, AstraZeneca, Bristol Myers Squib, Genmab, GSK, Roche, Novartis, and BeiGene. GS, JPM, NM, FZ, and AA report employment by and stock or stock options in AbbVie. EF reports employment by and stock or stock options in Genmab. FM reports serving in a consultancy role for Kite–Gilead, Roche, AbbVie, Bristol Myers Squibb, Janssen, Takeda, and Miltenyi; serving on speakers bureaus for Roche and Kite–Gilead; honoraria from AstraZeneca; and participation on an advisory board for AbbVie, Bristol Myers Squibb, Janssen, Kite–Gilead, Miltenyi, Roche, and Takeda. All other authors declare no competing interests.

Data sharing

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study report synopses, or statistical analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan, and execution of a Data Use Agreement. Data requests can be submitted at any time after approval in the USA and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select "Home".

Acknowledgments

We thank the participants and their families for their participation in this study. We also thank the participating study sites, investigators, data monitoring committee, and other research personnel for their support of this trial. We also wish to thank Anthony Wang and Jennifer Lord-Bessen (AbbVie) for participant-reported outcome analyses, Alena Vajikova (AbbVie) for study management, Yukun Li (AbbVie) for statistical analyses, and Ruiling Zhang (AbbVie) for statistical programming. The study was sponsored by Genmab and AbbVie. Medical writing assistance was provided by Kristina Y Aguilera (AbbVie) and Miriam Cohen (BioConnections), funded by Genmab and AbbVie.

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