Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (EPCORE NHL-1): a phase 2 cohort of a single-arm, multicentre study

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Summary

Background A standard of care and optimal duration of therapy have not been established for patients with multiply relapsed or refractory follicular lymphoma. The aim of this study was to evaluate epcoritamab, a novel CD3×CD20 bispecific antibody, in the third-line and later setting of follicular lymphoma.

Methods EPCORE NHL-1 is a multicohort, single-arm, phase 1–2 trial conducted at 88 sites across 15 countries. Here, we report the primary analysis of patients with relapsed or refractory follicular lymphoma in the phase 2 part of the trial, which included the pivotal (dose expansion) cohort and the cycle 1 optimisation cohort. Eligible patients were aged 18 years or older, had relapsed or refractory CD20^{+} follicular lymphoma (grade 1–3A), an Eastern Cooperative Oncology Group performance status of up to 2, and had received at least two previous lines of therapy (including an anti-CD20 monoclonal antibody and an alkylating agent or lenalidomide). Patients were treated with subcutaneous epcoritamab 48 mg in 28-day cycles: weekly in cycles 1–3, biweekly in cycles 4–9, and every 4 weeks until disease progression or unacceptable toxicity. To mitigate the risk and severity of cytokine release syndrome, in the pivotal cohort, cycle 1 consisted of a step-up dosing regimen of a 0·16-mg priming dose on day 1 and a 0·80-mg intermediate dose on day 8, followed by subsequent 48-mg full doses and prophylactic prednisolone 100 mg; in the cycle 1 optimisation cohort, a second intermediate dose of 3 mg on day 15, adequate hydration, and prophylactic dexamethasone 15 mg were evaluated during cycle 1 to further reduce risk and severity of cytokine release syndrome. Primary endpoints were independently reviewed overall response rate for the pivotal cohort and the proportion of patients with grade 2 or worse and any-grade cytokine release syndrome for the cycle 1 optimisation cohort. Analyses were done in all enrolled patients who had received at least one dose of epcoritamab. This study is registered with ClinicalTrials.gov, NCT03625037, and is ongoing.

Findings Between June 19, 2020, and April 21, 2023, 128 patients (median age 65 years [IQR 55–72]; 49 [38%] female and 79 [62%] male) were enrolled and treated in the pivotal cohort (median follow-up 17·4 months [IQR 9·1–20·9]). The overall response rate was 82·0% (105 of 128 patients; 95% CI 74·3–88·3), with a complete response rate of 62·5% (80 of 128; 95% CI 53·5–70·9). The most common grade 3–4 treatment-emergent adverse event was neutropenia in 32 (25%) of 128 patients. Grade 1–2 cytokine release syndrome was reported in 83 (65%) of 128 patients; grade 3 cytokine release syndrome was reported in two (2%). Immune effector cell-associated neurotoxicity syndrome was reported in eight (6%) of 128 patients (five [4%] grade 1; three [2%] grade 2). Between Oct 25, 2022, and Jan 8, 2024, 86 patients (median age 64 years [55–71]; 37 [43%] female and 49 [57%] male) were enrolled and treated in the cycle 1 optimisation cohort. The incidence of cytokine release syndrome was 49% (42 of 86 patients; eight [9%] grade 2; none of grade 3 or worse), with no reported immune effector cell-associated neurotoxicity syndrome.

Interpretation Epcoritamab monotherapy showed clinically meaningful activity in patients with multiply relapsed or refractory follicular lymphoma, and had a manageable safety profile.

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Introduction

Follicular lymphoma is the most common indolent non-Hodgkin lymphoma and, when advanced, is considered an incurable malignancy. Although some patients have an indolent course of disease and reach long-term remission after first-line treatment, others experience rapid disease progression and undergo increasingly treatment-refractory relapses of disease, with successively lower response rates and shorter times to next therapy.[1,2]

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Research in context

Evidence before this study

We searched PubMed on March 21, 2024, using the search terms "follicular lymphoma", "relapsed", "refractory", and "chemoimmunotherapy", "CAR T", "bispecific", or "treatment", filtered for "clinical trial" or "randomized controlled trial", for articles published in any language between Jan 1, 2010, and Jan 1, 2020. Before initiation of this study, few treatment options for patients with relapsed or refractory follicular lymphoma were available. Chemoimmunotherapy regimens like R-CHOP, R-bendamustine, and R-CVP were used; however, patients could become refractory to these therapies, and chemotherapy was associated with serious toxicities. Patients with relapsed or refractory follicular lymphoma in the MAGNIFY phase 3 trial (n=117; NCT01996865) were treated with rituximab and lenalidomide; 67% of evaluable patients had a response, with 36% reaching complete response. Response rates among patients with double refractory disease or early relapse were lower. 1-year progression-free survival with lenalidomide and rituximab was 66%. Emerging therapeutic modalities aimed at addressing the unmet need for patients who are resistant to rituximab or chemotherapy included T-cell-engaging therapies such as chimeric antigen receptor (CAR) T-cell therapies and bispecific T-cell engagers. At the time of EPCORE NHL-1 study initiation, CAR T therapies (axicabtagene ciloleucel [NCT03105336] and tisagenlecleucel [NCT03568461]) and CD3×CD20 bispecific antibodies (odronextamab [NCT02290951], mosunetuzumab [NCT02500407], and glofitamab [NCT03075696]) were being evaluated for the treatment of relapsed or refractory follicular lymphoma. Compared with CAR T therapies, bispecific antibodies offer off-the-shelf convenience and might be more easily accessible. Epcoritamab, a CD3×CD20 bispecific antibody, showed specific, highly potent antitumour activity in preclinical studies, inducing T-cell-mediated cytotoxicity against malignant CD20$^+$ B cells. Subcutaneous administration was found to be effective while lowering concentrations of plasma cytokines compared with intravenous administration. Based on these studies and the unmet need for safe, effective, and convenient treatments, the first-in-human study EPCORE NHL-1 was initiated.

Added value of this study

Results from the phase 2, pivotal cohort coupled with the cycle 1 optimisation cohort of the EPCORE NHL-1 trial provide evidence of the safety and activity of epcoritamab in the relapsed or refractory follicular lymphoma setting. Epcoritamab monotherapy led to deep, durable responses in a heavily pretreated population, including in patients with high-risk disease features or those in later lines of treatment. A large analysis of measurable residual disease (MRD) showed high rates of MRD negativity, which was associated with improved progression-free survival. The safety profile was consistent with previous reports of epcoritamab. In the optimisation cohort for relapsed or refractory follicular lymphoma, the optimised, three-stage step-up dosing regimen and simple measures of prophylactic dexamethasone and hydration yielded lower rates of cytokine release syndrome, with no immune effector cell-associated neurotoxicity syndrome reported, and preliminary response rates suggesting no loss of activity.

Implications of all the available evidence

Epcoritamab demonstrated clinically meaningful activity with manageable safety in patients with relapsed or refractory follicular lymphoma after at least two previous lines of systemic therapy. The optimal strategy for treatment duration, whether fixed dosing or treatment to progression, is not yet determined. As a novel subcutaneous therapy with a treatment-to-progression dosing strategy, epcoritamab is a potential alternative to current treatment options in this setting.

Patients with multiply relapsed follicular lymphoma need safe, novel therapies to provide deep and durable responses. There is no standard of care or optimal duration of therapy in these later-line settings. Patients with high-risk follicular lymphoma, such as disease progressing within 24 months of first-line treatment, or those with advanced age (≥ 65 years), comorbid conditions, higher Follicular Lymphoma International Prognostic Index, or more previous therapies, have particularly poor outcomes, with shorter remissions and higher mortality rates.[1,3,4]

T-cell-engaging therapies are a novel class of agents for the treatment of multiply relapsed follicular lymphoma. This class includes chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies that are approved or in development for the treatment of relapsed or refractory follicular lymphoma. The approved agents have been shown to be effective in their respective clinical trials; CAR T-cell therapies can also be beneficial due to the short treatment time. However, these therapies are either dosed intravenously, or, as with CAR T-cell therapy, are associated with high rates of toxicities and require specialised treatment centres to be administered safely; therefore, an unmet need exists for therapies that combine efficacy and safety with greater convenience. Epcoritamab is a subcutaneously administered CD3×CD20 bispecific antibody that induces T-cell-mediated cytotoxicity against malignant B cells.[5,6] It is approved for the treatment of several types of relapsed or refractory large B-cell lymphoma in the USA, Europe, Japan, and other regions.[7,8] The phase 1 part of this trial showed that epcoritamab was tolerable with promising activity in relapsed or refractory follicular lymphoma.[9] Here, we present the primary analysis of patients with relapsed or refractory follicular lymphoma treated with epcoritamab after at least two previous therapies in the phase 2 part of the EPCORE NHL-1 trial.

Methods

Study design and participants

The phase 1 study design and methods have been reported previously.[9] Phase 2 included two cohorts: pivotal (dose expansion) and cycle 1 optimisation. This open-label, single-arm study was conducted at 88 sites across 15 countries (66 sites across 14 countries for follicular lymphoma pivotal and cycle 1 optimisation cohorts; appendix pp 2–3). Patients aged 18 years or older (or 21 years in countries where this is the legal adult age) with CD20+ follicular lymphoma, histologically confirmed grade 1–3A, at least two previous lines of therapy (including an anti-CD20 monoclonal antibody and an alkylating agent or lenalidomide), relapsed or refractory to the last previous line of therapy, and an Eastern Cooperative Oncology Group (ECOG) performance status of up to 2 were enrolled. Key exclusion criteria included primary CNS lymphoma or known CNS involvement by lymphoma; known HIV infection (patients with HIV will be studied separately); known clinically significant cardiovascular disease; ongoing active infection requiring systemic treatment (excluding prophylactic treatment) at the time of enrolment or within 2 weeks before treatment; confirmed history or current autoimmune disease; previous therapy with an investigational bispecific antibody targeting CD3 and CD20; CAR T-cell therapy within 30 days before treatment; and pregnancy or breastfeeding (due to potential lymphocytopenia caused by IgG antibodies crossing the placenta or being expressed in breastmilk). Additional information on inclusion and exclusion criteria can be found in the appendix (pp 4–6).

The trial protocol was approved by site-specific institutional review boards or independent ethics committees before study initiation. The study was conducted in accordance with the International Council for Harmonisation E6(R2) guidelines on good clinical practice and the principles of the Declaration of Helsinki. All patients provided written informed consent. This study is registered with ClinicalTrials.gov, NCT03625037, and is ongoing.

Procedures

Patients received subcutaneous epcoritamab (Genmab, Valby, Denmark; Genmab US, Plainsboro, NJ, USA) in 28-day cycles: once weekly during cycles 1–3, once every 2 weeks during cycles 4–9, and once every 4 weeks during cycle 10 and beyond. Treatment continued until unacceptable toxicity or disease progression. In the pivotal cohort, cycle 1 step-up dosing, consisting of a 0·16-mg priming dose on day 1, a 0·80-mg intermediate dose on day 8, and subsequent 48-mg full doses, was used to mitigate the risk and severity of cytokine release syndrome. Prophylaxis included intravenous prednisolone 100 mg (or equivalent, including oral) given 30 min to 2 h before each epcoritamab dose, followed by 3 consecutive days of daily intravenous prednisolone 100 mg (or equivalent, including oral) after epcoritamab administration. Patients were hospitalised for 24 h after the first full dose for characterisation and monitoring of cytokine release syndrome.

In the cycle 1 optimisation cohort, a second intermediate dose of 3 mg on day 15, hydration (including a 500-mL intravenous isotonic solution and increased fluid intake), and dexamethasone 15 mg (given 30 min to 2 h before each epcoritamab dose, followed by 3 consecutive days of daily treatment) were evaluated as cytokine release syndrome prophylactic measures during cycle 1. Hospitalisation requirements for cytokine release syndrome monitoring after the first full dose of epcoritamab were removed for the cycle 1 optimisation cohort. Another arm of the cycle 1 optimisation cohort was planned to evaluate an alternative second intermediate dose. However, the arm was interrupted at an early stage to prioritise the recommended regimen shown here, because a preliminary analysis revealed a numerically lower rate of cytokine release syndrome compared with the alternative regimen; this was also supported by clinical pharmacology modelling. Furthermore, the 3-mg second intermediate step-up dose is more convenient in practice, because it is easier to prepare. There is no plan to share results from the interrupted arm due to the paucity of data generated.

See Online for appendix

Radiographic disease evaluation was based on ^{18}F-fluorodeoxyglucose PET and CT performed at weeks 6, 12, 18, 24, 36, and 48, and every 24 weeks thereafter. Measurable residual disease (MRD) negative status was assessed on longitudinal peripheral blood mononuclear cell samples at prespecified timepoints using the clonoSEQ (Adaptive Biotechnologies, Seattle, WA) next-generation sequencing assay. Screening tumour biopsies were used to identify trackable tumour clones; samples were quantified as tumour clones detected per one million nucleated cells (10^{-6}). MRD samples were collected at screening, on day 1 of cycles 3, 5, 7, 10, and 13, and every 6 months thereafter; samples were also collected at the time of confirmed complete response.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome were graded according to the American Society for Transplantation and Cellular Therapy criteria.[10] All adverse events were reported and assessments made at each visit, or more frequently if necessary. All adverse events were reported from the first dose of epcoritamab until 60 days after the last epcoritamab dose; if a serious adverse event was considered by the investigator to be related to treatment, reports could be made more than 60 days after the last dose of epcoritamab. Details on criteria for dose modification or treatment discontinuation are in the appendix (pp 6–7).

Outcomes

The primary endpoint for the pivotal cohort was overall response rate according to an independent review committee and Lugano criteria.[11] Overall response rate was defined as the proportion of patients who reached a best overall response of partial response or complete response at any time. In the cycle 1 optimisation cohort, the primary endpoints were the rate of grade 2 or worse cytokine release syndrome and the rate of any-grade cytokine release syndrome from the first dose of epcoritamab until 7 days after administration of the second 48-mg dose of epcoritamab.

Secondary endpoints of the pivotal cohort included complete response rate, time to response, time to complete response, duration of response, duration of complete response, progression-free survival, overall survival, time to next therapy, adverse events, laboratory values, and MRD-negativity rate as of the data cutoff date.

Secondary endpoints of the cycle 1 optimisation cohort included rates of grade 2 or worse cytokine release syndrome and any-grade cytokine release syndrome after the first 48-mg dose and overall, adverse events, laboratory values, overall and complete response rates as assessed by the investigator, and MRD-negativity rate as of the data cutoff date.

Additional secondary endpoints are listed in the appendix (p 7) and will be reported elsewhere.

Prespecified subgroup analyses of response outcomes were planned for the pivotal cohort, including age, sex, number of previous lines of treatment, refractoriness to last previous therapy, double refractoriness, progression within 2 years of first therapy, and Follicular Lymphoma International Prognostic Index.

A landmark analysis was performed at cycle 3, day 1 for all MRD-evaluable patients as a post hoc analysis related to the secondary endpoint of MRD-negativity rate.

Exploratory analyses were performed to assess interleukin 6 (IL-6) levels in circulation after epcoritamab administration, which can be elevated in the context of cytokine release syndrome. Other cytokines assessed included interleukin 10, interferon γ, and tumor necrosis factor.

Patient-reported outcomes evaluated by the Functional Assessment of Cancer Therapy—Lymphoma and EQ-5D-3L assessments are reported separately.[12]

Statistical analysis

A target sample size of 128 patients was planned for the pivotal cohort to provide approximately 90% power to detect an overall response rate of greater than 50% with a two-sided significance level of 0·05. In the cycle 1 optimisation cohort, a sample size of 80 patients with the selected step-up dose regimen was planned to provide greater than 80% power to detect a true event rate of cytokine release syndrome of grade 2 or worse of at least 2%. In each cohort, efficacy analyses were based on the full analysis set, and safety analyses were based on the safety analysis set, each consisting of all enrolled patients who had received at least one dose of epcoritamab. The primary analysis of overall response rate was assessed by an independent review committee per Lugano criteria in the full analysis set. The overall response rate and the corresponding exact 95% CI were summarised. In the optimisation cohort, efficacy analyses were based on investigator assessment per Lugano criteria. MRD analyses were based on patients in the full analysis set with at least one baseline or on-treatment MRD result and baseline MRD not negative. Analyses were carried out using SAS version 9.4 or higher. Sensitivity analyses for progression-free survival and overall survival were carried out based on an adjusted population excluding patients with deaths on study related to COVID-19. A conservative approach was taken to identify patients who died due to a cause related to COVID-19; deaths resulting from a clinically compatible illness in an individual with probable or confirmed COVID-19 were censored unless there was a clear alternative cause of death that could not be related to COVID-19. Additional details on censoring are available in the appendix (p 7). Time-to-event endpoints (eg, duration of response, duration of complete response, progression-free survival, and overall survival) were analysed in the full analysis set using Kaplan–Meier estimates (median time and 95% CI). Safety endpoints were summarised using frequency and percentages based on the safety analysis set, consisting of all patients who received at least one dose of epcoritamab.

Role of the funding source

The funders of this study had a role in study design, data collection, data analysis, and data interpretation, and were involved in the writing, revision, and approval of this manuscript.

Results

From June 19, 2020, to data cutoff on April 21, 2023, 128 patients with follicular lymphoma (median age 65 years [IQR 55–72]; 49 [38%] female and 79 [62%] male) were enrolled in the pivotal cohort globally. Demographics and baseline characteristics are shown in table 1. Further information on previous systemic therapies of enrolled patients is provided in the appendix (p 8).

At a median follow-up of 17·4 months (IQR 9·1–20·9), 47 (37%) of 128 patients remained on treatment (figure 1). The most common reasons for discontinuation were progressive disease in 44 (34%) patients and adverse events in 24 (19%) patients. Patients initiated a median of eight cycles of epcoritamab (IQR 4–16). Median relative dose intensities across the different dose schedules (ie, weekly, biweekly, or every 4 weeks) were between 98·6% (IQR 90·9–100·0) and 100·0% (92·3–100·0).

The overall response rate was 82·0% (95% CI 74·3–88·3; 105 of 128 patients); 62·5% of patients (95% CI 53·5–70·9; 80 of 128) had a complete response. Responses were observed in all prespecified subgroups,

	Pivotal cohort (n=128)	Cycle 1 optimisation cohort (n=86)
Age, years	65 (55–72)	64 (55–71)
Sex		
Female	49 (38%)	37 (43%)
Male	79 (62%)	49 (57%)
Eastern Cooperative Oncology Group performance status		
0	70 (55%)	52 (60%)
1	51 (40%)	34 (40%)
2	7 (5%)	0
Creatinine clearance by Cockcroft–Gault method, mL/min		
≥90	52 (41%)	35 (41%)
≥60 to <90	54 (42%)	37 (43%)
≥45 to <60	22 (17%)	14 (16%)
Ann Arbor stage		
I	5 (4%)	0
II	14 (11%)	7 (8%)
III	32 (25%)	27 (31%)
IV	77 (60%)	52 (60%)
Follicular Lymphoma International Prognostic Index at inclusion*		
0 or 1	17 (13%)	11 (13%)
2	31 (24%)	31 (36%)
3–5	78 (61%)	44 (51%)
β2 microglobulin†		
High	79 (62%)	NA
Normal	45 (35%)	NA
Bulky disease		
≤6 cm	95 (74%)	69 (80%)
>6 cm	33 (26%)	17 (20%)
Bone marrow involvement per investigator's assessment	38 (30%)	21 (24%)
Time from diagnosis to first dose of epcoritamab, years	6 (3–11)	8 (5–11)
Time from end of previous line of therapy to first dose of epcoritamab, months	5 (2–17)	9 (3–28)
Time from end of last anti-CD20 therapy to first dose of epcoritamab, months	10 (3–22)	10 (4–32)
Number of previous lines of therapy	3 (2–4)	2 (2–3)
Two	47 (37%)	45 (52%)
Three	41 (32%)	24 (28%)
Four or more	40 (31%)	17 (20%)
Progression within 24 months of initiating first-line chemoimmunotherapy	54 (42%)	36 (42%)
Progression within 24 months of initiating any first-line therapy	67 (52%)	42 (49%)
Double refractory disease‡§	90 (70%)	54 (63%)
Primary refractory disease‡	69 (54%)	38 (44%)
Refractory to previous anti-CD20 therapy‡	101 (79%)	67 (78%)
Refractory to last previous systemic therapy‡	88 (69%)	49 (57%)
Previous chimeric antigen receptor T-cell therapy	6 (5%)	6 (7%)

Data are median (IQR) or n (%). NA=not available. *Follicular Lymphoma International Prognostic Index was unknown for one patient and not applicable for one patient (patient found to have transformed diffuse large B-cell lymphoma after screening tumour biopsy). †β2 microglobulin was missing for four patients. ‡Refractory is defined as disease that either progressed during therapy or progressed within 6 months of completion of therapy. §Double refractory is defined as disease refractory to both an anti-CD20 monoclonal antibody and an alkylating agent.

Table 1: **Demographics and baseline clinical characteristics**

including those with high-risk disease features (figure 2). Expectedly lower response rates were observed in patients with four or more previous lines of treatment or patients who were refractory to their last systemic therapy. Among six patients with previous CAR T-cell treatment, four had a response, three of whom had a complete response. Median time to response was 1·4 months (IQR 1·3–1·5) and median time to complete response was 1·5 months (1·4–2·8; appendix p 13). Among 49 responders treated in cycle 10 and beyond, 45 (92%) maintained response with epcoritamab administered every 4 weeks at data cutoff.

An estimated 58·4% (95% CI 46·4–68·7) of patients with response and 72·2% (57·6–82·5) of patients with complete response remained in response and complete response at 18 months after first response or complete response, respectively (appendix p 14). Additionally, at 18 months from initiation of therapy, an estimated 49·4% (39·0–59·1) of all patients (figure 3A) and 73·8% (60·1–83·4) of patients with complete response (figure 3B) were progression free. MRD was evaluable for 91 (71%) of 128 patients; of these, 61 (67%) patients were MRD negative. Among patients who were MRD negative, rates of progression-free survival were higher compared with patients that were not MRD negative and were similar across prespecified high-risk subgroups (figure 3C, appendix p 15). Among 77 MRD-evaluable patients in the cycle 3, day 1 landmark analysis, results similarly showed higher rates of progression-free survival among patients who were MRD negative (figure 3D). An estimated 70·2% (60·4–78·0) of all patients were alive at 18 months (figure 3E). Progression-free survival and overall survival improved when a post hoc sensitivity analysis adjusting for COVID-19 was performed (appendix p 16). At 18 months, an estimated 63·3% (53·7–71·4) of all patients had not initiated another line of antilymphoma therapy.

Treatment-emergent adverse events that were reported in at least 10% of patients are summarised by grade in table 2. The most common treatment-emergent adverse events were cytokine release syndrome (85 [66%] of 128), injection-site reaction (73 [57%]), COVID-19 (including COVID-19 pneumonia; 51 [40%]), and fatigue (39 [30%]).

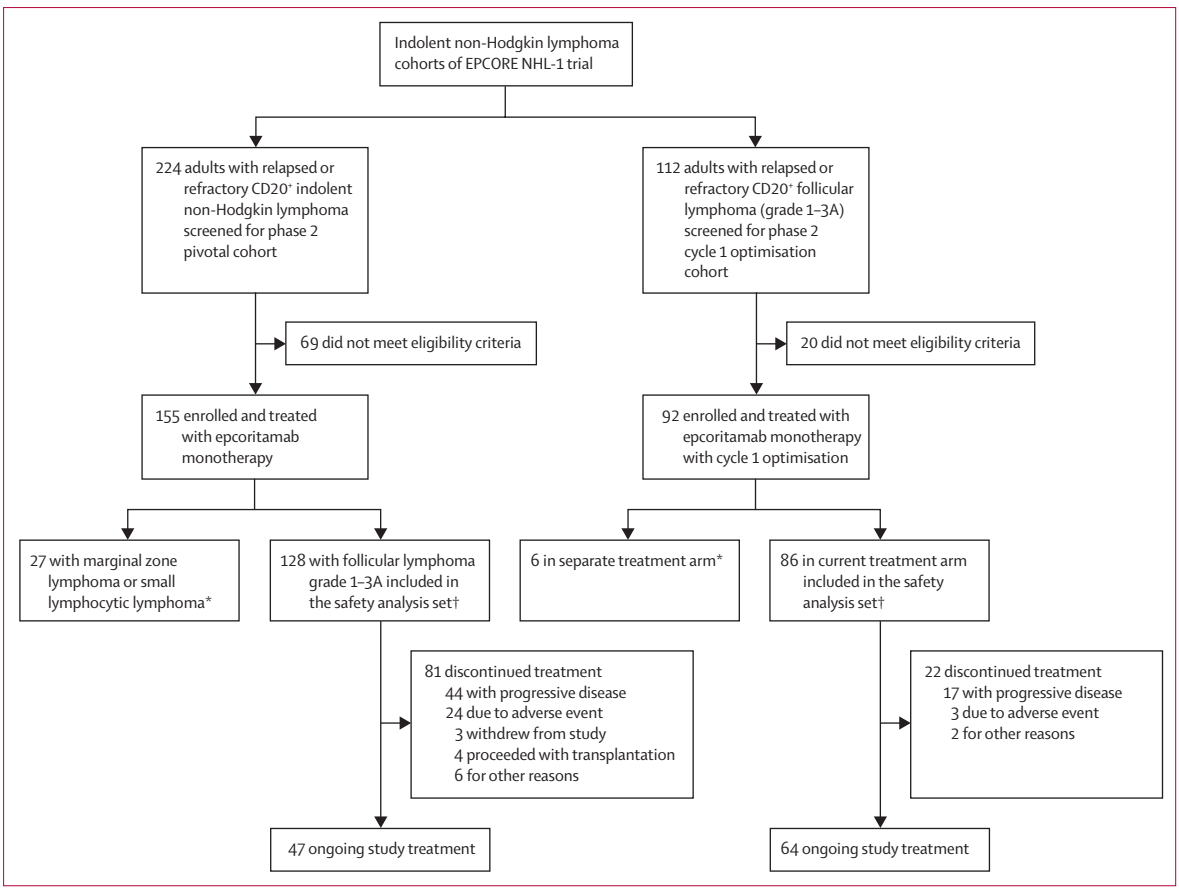


Figure 1: **Trial profile**
*Patients are not included in this analysis. †Includes all patients who received at least one dose of study treatment.

Treatment-emergent adverse events leading to treatment discontinuation occurred in 24 (19%) of 128 patients (appendix p 9). Infections led to treatment discontinuation in 17 (13%) of 128 patients: COVID-19 (including COVID-19 pneumonia) in 12 (9%) patients; hepatitis E in two (2%) patients; and pneumonia, sepsis from *Pseudomonas aeruginosa*, and sinusitis in one (1%) patient each. Other reasons for discontinuation were angioimmunoblastic T-cell lymphoma, cardiopulmonary failure (with COVID-19), diarrhoea, enteritis, fatigue and malaise, general physical health deterioration (with sinusitis), interstitial lung disease, malignant peritoneal neoplasm, and pneumonitis in one patient each. All grade 3 and worse events with total incidence of less than 10% are shown in the appendix (pp 10–11).

Most patients with reported cytokine release syndrome had grade 1 (51 [40%] of 128 patients) or grade 2 (32 [25%]) events; two (2%) patients had grade 3 cytokine release syndrome, and no grade 4 or 5 events were reported. Rates of cytokine release syndrome by dosing interval are shown in the appendix (p 17). 76 (60%) of 126 patients had cytokine release syndrome after the first full dose (median time to onset, 15·3 h [IQR 9·5–22·1]). Among all 128 patients, 31 (24%) were treated with tocilizumab and 17 (13%) were treated with a corticosteroid (beyond the protocol-required prophylaxis). All events resolved (median time to resolution, 2 days [1–5]) and none led to treatment discontinuation. Immune effector cell-associated neurotoxicity syndrome was observed in eight (6%) of 128 patients; five (4%) patients had grade 1 events, and three (2%) patients had grade 2 events. The median time to onset from most recent dose was 3·5 days (2·0–7·5); all immune effector cell-associated neurotoxicity syndrome events resolved in a median of 2·0 days (1·0–4·5), and none led to epcoritamab discontinuation. No clinical tumour lysis syndrome events were reported.

Of 128 total patients, 36 (28%) patients had neutropenia (excluding febrile neutropenia), and 23 (18%) required treatment for neutropenia with granulocyte colony-stimulating factor (GCSF); median time from first dose to onset was 63·5 days (IQR 32·5–106·5), and median time to resolution was 27·5 days (8·5–54·5). No patients discontinued treatment due to treatment-emergent neutropenia. Febrile neutropenia was observed in four (3%) of 128 patients; all events were grade 3, and all patients required treatment with GCSF. Fatal treatment-emergent

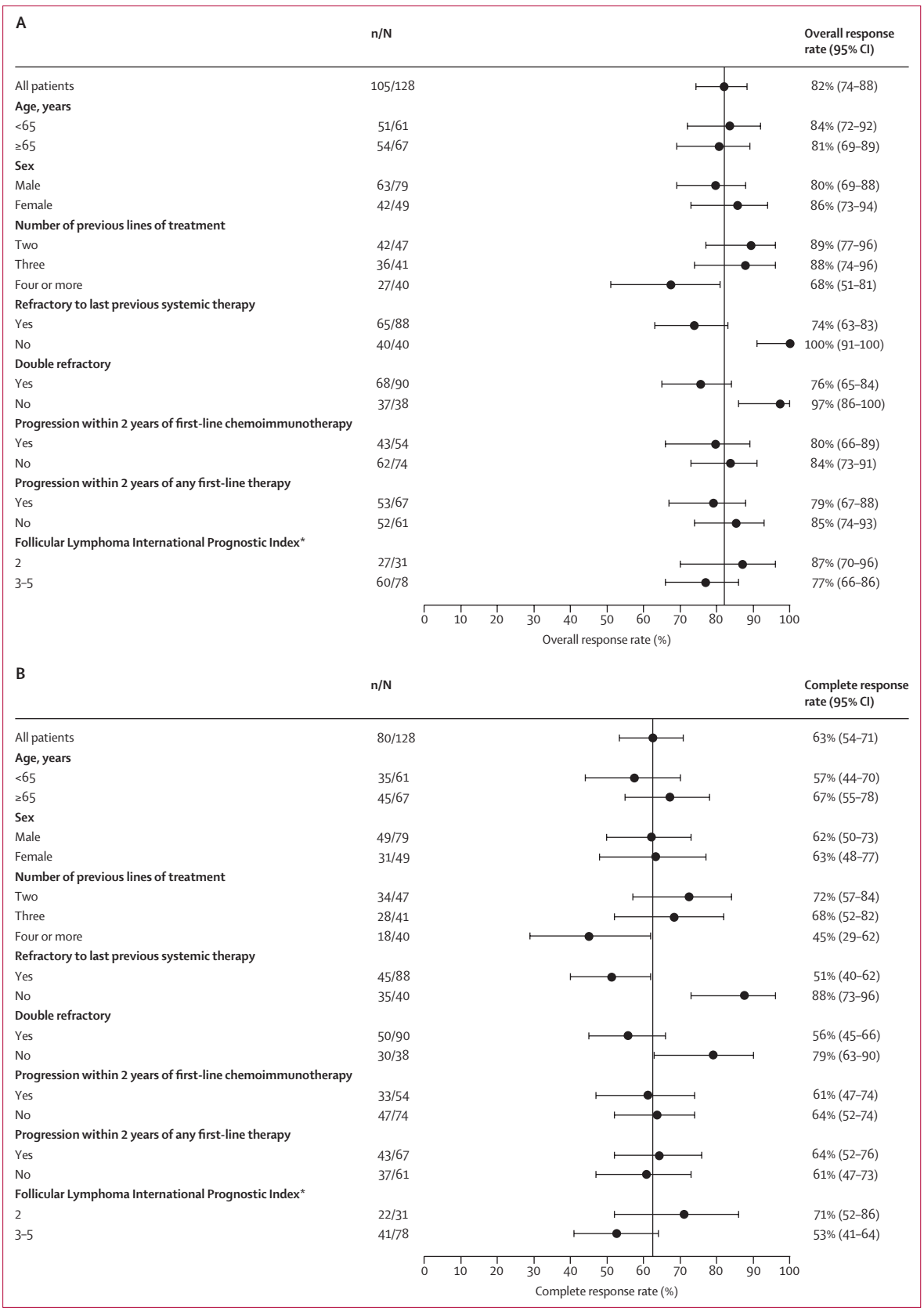
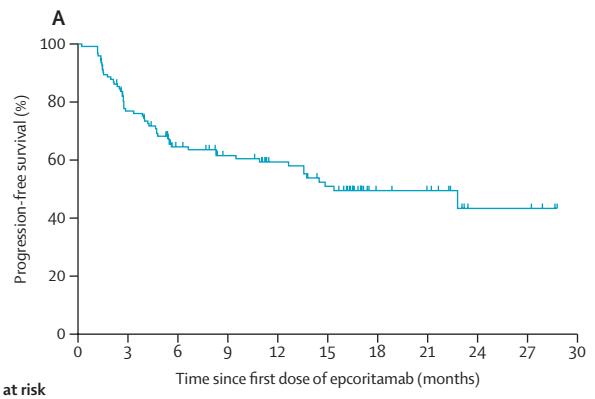
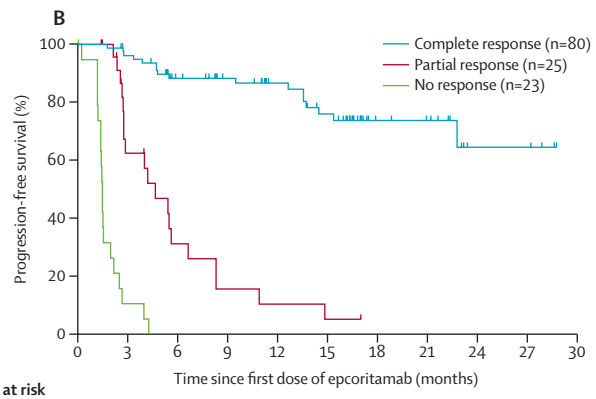


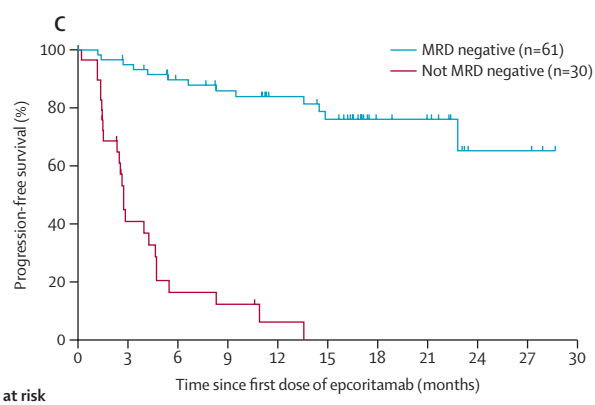
***Figure 2*: Subgroup analyses of response outcomes in the pivotal cohort**
Overall response rate (A) and complete response rate (B). *Follicular Lymphoma International Prognostic Index of 0 or 1 was not included in subgroup analyses due to the small numbers of patients with these scores.



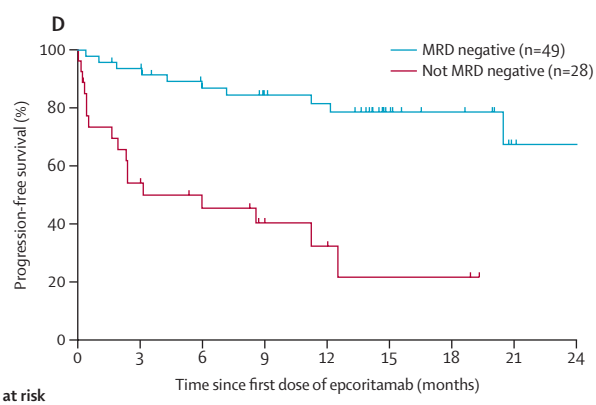
Number at risk (number censored)											
Pivotal cohort	128	90	67	57	43	35	14	12	4	4	0
	(0)	(10)	(19)	(26)	(38)	(40)	(60)	(62)	(69)	(69)	(73)



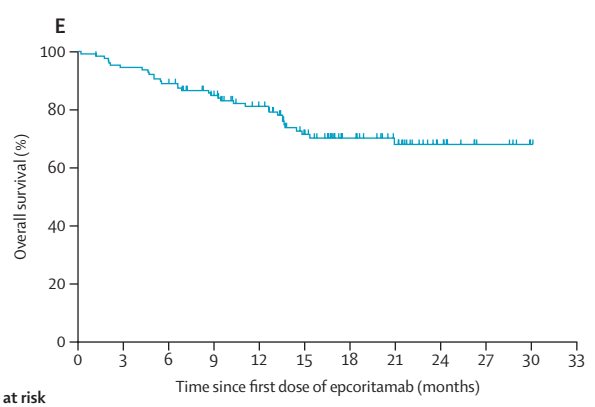
Number at risk (number censored)											
Complete response	80	75	61	54	41	34	14	12	4	4	0
	(0)	(2)	(10)	(17)	(29)	(31)	(50)	(52)	(59)	(59)	(63)
Partial response	25	13	6	3	2	1	0	0	0	0	0
	(0)	(4)	(5)	(5)	(5)	(5)	(6)	(6)	(6)	(6)	(6)
No response	23	2	0	0	0	0	0	0	0	0	0
	(0)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)



Number at risk (number censored)											
MRD negative	61	56	48	43	33	29	13	11	3	3	0
	(0)	(2)	(7)	(10)	(19)	(20)	(36)	(38)	(45)	(45)	(48)
Not MRD negative	30	10	4	3	1	0	0	0	0	0	0
	(0)	(4)	(4)	(4)	(5)	(5)	(5)	(5)	(5)	(5)	(5)



Number at risk (number censored)									
MRD negative	49	44	38	31	28	15	10	4	3
	(0)	(2)	(6)	(11)	(13)	(25)	(30)	(35)	(36)
Not MRD negative	28	14	11	6	4	2	2	0	0
	(0)	(2)	(4)	(7)	(8)	(9)	(9)	(11)	(11)



Number at risk (number censored)											
Pivotal cohort	128	120	113	97	82	60	41	31	15	6	1	0
	(0)	(1)	(1)	(12)	(23)	(36)	(54)	(63)	(79)	(88)	(93)	(94)

adverse events were reported in 13 patients and included COVID-19 in six (5%) of 128 patients, and pneumonia, sepsis from *Pseudomonas aeruginosa*, lymphoma transformation, myelodysplastic syndrome (pre-existing condition), interstitial lung disease, organising pneumonia, and cardiopulmonary failure in one patient each. No deaths were considered by the investigator to be related to treatment. Onset times to fatal COVID-19 infections ranged from 43 days to 403 days since first dose. Exposure-adjusted incidence rates of COVID-19 for patients in the pivotal cohort are shown in the appendix (p 12). The exposure-adjusted incidence of COVID-19 was much higher after the emergence of omicron and subsequent variants, regardless of the epcoritamab dosing period.

From Oct 25, 2022, to data cutoff on Jan 8, 2024, 86 patients (median age 64 years [IQR 55–71]; 37 [43%] female and 49 [57%] male) were enrolled in the cycle 1 optimisation cohort globally and treated with an optimised cycle 1 step-up dosing regimen (figure 1). Median follow-up was 5·7 months (IQR 2·9–7·2). Demographics and baseline characteristics were consistent with those of patients enrolled in the pivotal cohort (table 1).

Clinically meaningful reductions in the rate and severity of cytokine release syndrome were observed compared with the pivotal cohort, with cytokine release syndrome reported in 42 (49%) of 86 patients; all events were grade 1 or 2 (34 [40%] and eight [9%] patients, respectively), with no grade 3 or worse events. Rates of cytokine release syndrome by dosing interval are shown in the appendix (p 18); cytokine release syndrome events occurred most commonly after the first full dose, with 30 (37%) of 82 patients experiencing cytokine release syndrome during that interval (median time to onset, 60·7 hours [IQR 36·6–84·3]). Among all 86 patients, tocilizumab and corticosteroid treatment (beyond the protocol-required prophylaxis) were administered to ten (12%) and 11 (13%) patients, respectively. Median time to cytokine release syndrome resolution was 2 days (IQR 1–3); no patients discontinued epcoritamab due to cytokine release syndrome and all events resolved. More than half of patients (44 [54%] of 82) were not proactively hospitalised for monitoring at first full dose. Consistent with the clinical findings, IL-6 concentrations 24 h after the first 48-mg dose were lower with cycle 1 optimisation versus the pivotal cohort; median IL-6 and other cytokine concentrations in the cycle 1 optimisation cohort

	Grade 1–2	Grade 3	Grade 4	Grade 5
Pivotal cohort (n=128)				
Cytokine release syndrome	83 (65%)	2 (2%)	0	0
Injection-site reaction*	73 (57%)	0	0	0
COVID-19*	27 (21%)	18 (14%)	0	6 (5%)
Fatigue	36 (28%)	3 (2%)	0	0
Neutropenia*	4 (3%)	16 (13%)	16 (13%)	0
Diarrhoea	32 (25%)	2 (2%)	0	0
Pyrexia	29 (23%)	3 (2%)	0	0
Headache	25 (20%)	0	0	0
Cough	22 (17%)	0	0	0
Nausea	22 (17%)	0	0	0
Constipation	20 (16%)	0	0	0
Anaemia*	11 (9%)	8 (6%)	0	0
Arthralgia	17 (13%)	1 (1%)	0	0
Peripheral oedema	18 (14%)	0	0	0
Dyspnoea†	17 (13%)	0	0	0
Upper respiratory tract infection	17 (13%)	0	0	0
Insomnia	16 (13%)	0	0	0
Lymphopenia*	2 (2%)	5 (4%)	9 (7%)	0
Thrombocytopenia*	9 (7%)	2 (2%)	5 (4%)	0
Back pain	14 (11%)	1 (1%)	0	0
Dizziness	14 (11%)	0	0	0
Urinary tract infection	8 (6%)	5 (4%)	0	0
Cycle 1 optimisation cohort (n=86)				
Cytokine release syndrome	42 (49%)	0	0	0
Injection-site reaction*	28 (33%)	0	0	0
Constipation	18 (21%)	0	0	0
COVID-19*	13 (15%)	5 (6%)	0	0
Neutropenia*	1 (1%)	9 (10%)	8 (9%)	0
Fatigue	17 (20%)	0	0	0
Cough	14 (16%)	0	0	0
Headache	11 (13%)	1 (1%)	0	0
Peripheral oedema	12 (14%)	0	0	0
Pyrexia	12 (14%)	0	0	0
Anaemia*	9 (10%)	2 (2%)	0	0
Arthralgia	11 (13%)	0	0	0
Lymphopenia*	1 (1%)	7 (8%)	3 (3%)	0
Nausea	10 (12%)	1 (1%)	0	0
Diarrhoea	10 (12%)	0	0	0
Abdominal pain	9 (10%)	0	0	0
Insomnia	9 (10%)	0	0	0

Data are n (%). Median follow-up was 17·4 months in the pivotal cohort and 5·7 months in the cycle 1 optimisation cohort. Events in at least 10% of patients by worst grade are shown. All grade 3 and worse events are shown in the appendix (pp 10–11). *Based on combined terms: injection-site reaction includes injection-site reaction, erythema, rash, pruritus, inflammation, pain, oedema, nodule, and bruising; COVID-19 includes COVID-19, COVID-19 pneumonia, post-acute COVID-19 syndrome, and positive SARS-CoV-2 test; neutropenia includes neutropenia and decreased neutrophil count; anaemia includes anaemia and decreased serum ferritin; lymphopenia includes lymphopenia and decreased lymphocyte count; thrombocytopenia includes thrombocytopenia and decreased platelet count. †One additional patient had a dyspnoea adverse event of unknown grade.

Table 2: **Treatment-emergent adverse events**

Figure 3: **Progression-free survival and overall survival in the pivotal cohort**
Kaplan–Meier curves of progression-free survival overall (A), progression-free survival by response outcomes (B), progression-free survival by MRD status (C), progression-free survival by MRD status in a cycle 3, day 1 landmark analysis (D), and overall survival (E) for the pivotal cohort. All enrolled patients (n=128) are included in parts A, B, and E. MRD-evaluable patients overall are included in part C (n=91). MRD-evaluable patients at cycle 3, day 1 are included in part D (n=77). MRD=measurable residual disease.

remained low (appendix pp 19–24). No immune effector cell-associated neurotoxicity syndrome events were observed. Treatment-emergent adverse events reported in at least 10% of patients are summarised by grade in table 2. An overview of treatment-emergent adverse events and grade 3 and worse events is presented in the appendix (pp 9–11).

The overall response rate in the cycle 1 optimisation cohort was 86·0% (95% CI 76·9–92·6; 74 of 86 patients); 64·0% of patients had a complete response (52·9–74·0; 55 of 86 patients). The median time to response was 1·4 months (IQR 1·4–1·5) and median time to complete response was 1·5 months (1·4–2·8). Of 44 MRD-evaluable patients, 28 (64%) were MRD negative.

Discussion

In the EPCORE NHL-1 study, we enrolled patients with broad eligibility criteria and included patients with heavily pretreated, highly refractory, high-risk disease, as well as patients with an ECOG performance status of 2 or impaired renal function (creatinine clearance of 45–60 mL/min). In the pivotal cohort, epcoritamab elicited deep and durable responses, with overall and complete response rates of 82·0% and 62·5%, respectively. Response rates were consistently high across most subgroups, independent of high-risk disease features. Complete responses were observed in approximately half of patients receiving epcoritamab in the fifth or later line and those refractory to their last line of therapy, indicating that epcoritamab can provide potent antitumour activity in heavily pretreated, highly refractory patients. As expected, responses were higher in patients with less refractory disease, with most of these patients reaching a complete response: non-double refractory, 78·9%; non-refractory to last therapy, 87·5%. Additionally, an association between MRD and progression-free survival was seen.

The safety profile of epcoritamab in the pivotal cohort was manageable and similar to reports of epcoritamab monotherapy in the pivotal EPCORE NHL-1 diffuse large B-cell lymphoma cohort.[7] With this heavily pretreated relapsed or refractory follicular lymphoma patient population, neutropenia was an expected adverse event. Neutropenia events were manageable, and no patients discontinued epcoritamab treatment due to neutropenia. Quality of life did not appear to be affected by adverse events.[12] Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome were similarly manageable in the follicular lymphoma pivotal cohort, with mostly low-grade events, and safety was further optimised in the cycle 1 optimisation cohort. The incorporation of a second intermediate dose (3 mg) into the cycle 1 step-up dosing regimen, prophylactic dexamethasone as the preferred corticosteroid (due to prolonged duration of action and better CNS penetration than prednisolone), and adequate hydration during cycle 1 led to improved safety through mitigation of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome. Rates and severity of cytokine release syndrome were substantially reduced compared with the pivotal cohort, with a clinically meaningful reduction in grade 2 events (9% *vs* 25%) and no grade 3 or worse events reported. Of note, because hospitalisation was not mandated in the cycle 1 optimisation cohort, more than half of patients were not pre-emptively hospitalised for cytokine release syndrome monitoring after the first full dose, demonstrating that cytokine release syndrome diagnosis was not affected by removing mandatory hospitalisation and that cytokine release syndrome can be identified in a timely manner and managed successfully in patients treated in the outpatient setting, with reactive hospitalisation utilised as clinically appropriate. No immune effector cell-associated neurotoxicity syndrome was observed in the cycle 1 optimisation cohort. Results from exploratory analyses of IL-6 concentrations were consistent with lower observed rates and severity of cytokine release syndrome. Preliminary response rates indicate that activity was not affected by these mitigation strategies; however, time-to-event outcomes were limited due to short follow-up.

Patients with multiply relapsed or refractory follicular lymphoma need treatment options with improved safety and efficacy, especially in later lines of treatment when responses are harder to elicit. Overall and complete response rates of third-line patients in the pivotal cohort compare favourably to those reported for standard third-line treatment: 89·4% versus approximately 70% and 72·3% versus approximately 40%, respectively.[1,2] The clinical activity and safety of epcoritamab monotherapy were similar to other CD3×CD20 bispecific antibodies in relapsed or refractory follicular lymphoma, although cross-trial comparisons must be interpreted with caution due to differences in trial design, patient populations, and timing.[13–18] Epcoritamab might improve practice efficiencies compared with other CD3×CD20 bispecific antibodies, which currently require intravenous administration that can negatively affect patient experience and health-care resource utilisation.[19,20] Furthermore, the optimal duration of CD3×CD20 bispecific antibody treatment in lymphomas is not yet determined; in contrast to fixed-duration strategies of other therapies, the epcoritamab dosing schedule employs a treatment-to-progression strategy, which might allow for continued therapy in patients who are deriving benefit with a goal of maintaining response. Treatment to progression could help address current challenges of potential relapse after fixed-duration antilymphoma therapy by providing continuous T-cell engagement. T-cell function with persistent antigen stimulation has not been evaluated;[21] assays exploring T-cell exhaustion and the impact on treatment strategies are in development. Although CAR T-cell therapies tisagenlecleucel and axicabtagene ciloleucel have shown similarly high complete response rates (68–79%) in a generally fitter patient population

with relapsed or refractory follicular lymphoma, these therapies require conditioning with lymphodepleting therapies, and access is limited to specialised treatment centres.[22–25] The safety profile of epcoritamab, including immune effector cell-associated neurotoxicity syndrome and cytokine release syndrome incidence and severity with the cycle 1 optimisation regimen, is similar or favourable to CAR T-cell therapies, although confounding factors such as differences in patient populations and trial methods should be considered.[22–25] Clinically meaningful outcomes observed in this trial are further emphasised by the majority of evaluable patients, including those in high-risk subgroups, reaching MRD negativity, which was associated with improved long-term outcomes. To our knowledge, these results represent the largest analysis of MRD across studies of T-cell-engaging therapies in relapsed or refractory follicular lymphoma. MRD is being further evaluated as a potential surrogate of efficacy with epcoritamab.

This study was conducted during the peak of the COVID-19 pandemic when highly infectious variants emerged, when a global surge in infections was noted in patients with haematological malignancies, including follicular lymphoma, and when pandemic-related social restrictions were lifted in many regions.[26–29] Haematological malignancies and associated treatments, including B-cell-depleting therapies, such as monoclonal antibodies, bispecific antibodies, and CAR T-cell therapies, have been associated with an increased risk of morbidity and mortality due to infections, including COVID-19.[29–33] Multiple established risk factors for severe COVID-19 outcomes were identified in the study population; all patients had haematological malignancies and were actively receiving cancer treatment, and several patients had additional risk factors of advanced age and comorbid conditions, such as chronic lung disease. Similar to COVID-19 outcomes in the pivotal cohort, 35% of patients treated with odronextamab in the ELM-2 study had COVID-19, including 6% with fatal (grade 5) events.[13] Although variant testing was not performed, disproportionally higher rates of fatal infections were seen in this EPCORE NHL-1 FL trial relative to other epcoritamab trials due to enrolment during the peak of COVID-19 omicron incidence, when mortality rates increased for patients with lymphoma. Sensitivity analyses adjusting for COVID-19-associated deaths indicate that the pandemic might have impacted results of time-to-event analyses, including progression-free survival and overall survival. The timing of study conduct should be considered to contextualise the impact of COVID-19 on the trial results as research in this area evolves.

The limitations of EPCORE NHL-1 include those associated with an open-label, single-arm design, with no comparator or control group. Observed outcomes, therefore, could have been influenced by other factors, such as natural progression of disease or concomitant medications (although no concomitant anti-lymphoma medications were permitted). Due to the single-arm design, there are inherent limitations to assessing the relatedness of treatment-emergent adverse events. Additionally, no head-to-head trials have compared strategies for the optimal treatment duration for follicular lymphoma. In the absence of head-to-head data, we conducted an unanchored, matching-adjusted indirect comparison of epcoritamab with standard-of-care therapies by adjusting for imbalances in key baseline characteristics of the 128 patients with relapsed or refractory follicular lymphoma in the pivotal cohort discussed here and 206 real-world patients with relapsed or refractory follicular lymphoma treated with standard-of-care therapies between 2014 and 2020 from the SCHOLAR-5 study.[2] After adjustment, patients treated with epcoritamab had higher response rates and improved progression-free survival and overall survival versus standard of care.[34] Studies maximising the efficacy of epcoritamab in combination with standards of care with fixed-duration treatment schedules are ongoing in first-line and second-line follicular lymphoma. Response rates were consistently high across patient subgroups, although the smaller sample sizes, and therefore reduced statistical power, for certain subgroups should be noted. Due to this study population, results cannot be generalised to patients with less advanced follicular lymphoma. Additionally, with a heavily pretreated patient population, there is potential for confounding from previous therapies. Ethnicity was not reported for patients enrolled outside of the USA. The objective of cycle 1 optimisation was to reduce incidence and severity of cytokine release syndrome, which was accomplished. Although cycle 1 optimisation is not anticipated to impact efficacy or long-term safety, given the shorter duration of study follow-up compared with the pivotal cohort, direct comparisons of other results should not be made at this time. Given the chronic nature of follicular lymphoma, the median follow-up periods are relatively short. Additional follow-up is planned.

In summary, results from EPCORE NHL-1 showed robust, clinically meaningful efficacy, including deep and durable responses and high rates of MRD negativity in the largest known analysis of T-cell-engaging therapies in patients with relapsed or refractory follicular lymphoma. Cycle 1 optimisation further improved the safety profile, in addition to removing mandatory hospitalisation. These results indicate that epcoritamab has the potential to be an important therapy for the treatment of relapsed or refractory follicular lymphoma. Epcoritamab in combination with rituximab and oral lenalidomide is currently being evaluated in phase 3 studies of patients with relapsed or refractory follicular lymphoma (EPCORE FL-1; NCT05409066), as well as in the first-line setting (EPCORE FL-2; NCT06191744).

Contributors

Study design: TA, EF, and BE. Literature search: KML and JMV. Study investigators: KML, UV, WJ, PJL, EG, AS, JHC, BH, HT, RC, DJL, CO,

MH, MRC, J-MS, TC, SL, MEDC, CT, and JMV. Patient enrolment: KML, UV, WJ, PJL, EG, AS, JHC, BH, HT, RC, DJL, CO, MH, MRC, J-MS, TC, SL, MEDC, CT, and JMV. Collection and assembly of data: KML, UV, WJ, PJL, EG, AS, JHC, BH, HT, RC, DJL, CO, MH, MRC, J-MS, TC, SL, MEDC, DG, IA, YL, EF, BE, CT, and JMV. Data analysis: DG, IA, YL, MHD, DH, EF, and BE. Data verification: DG, IA, YL, DH, EF, and BE. All authors contributed to data interpretation, manuscript preparation, manuscript review and revisions, and final approval of the manuscript.

Declaration of interests

KML declares being a member of the Epcoritamab Global Council on behalf of Genmab; a consulting or advisory role for AbbVie, BeiGene, BMS, Genmab, Kite/Gilead, and Roche; participation in speakers bureaus from AbbVie and BMS; research funding (paid to institution) from AbbVie, ADC Therapeutics, AstraZeneca, BeiGene, BMS, CellCentric, Genmab, Janssen, Kite/Gilead, MorphoSys, MSD, Nurix, Regeneron, Roche, Step Pharma, and Viracta; and travel expenses from BMS. UV declares participation on an advisory board for AbbVie, Bayer, Genmab, Gilead, and Novartis; and lecture fees from AbbVie, Incyte, Janssen, Regeneron, Roche, and Servier. WJ declares research funding and consultancy fees from AbbVie and Roche. PJL declares research grants from Takeda and Servier; advisory honoraria from BMS, Roche, Takeda, Genmab, AbbVie, Incyte, Regeneron, and Sandoz; and consultancy honoraria from Y-mAbs Therapeutics. EG declares congress or travel fees or hospitality from AbbVie, Amgen, Gilead, Roche, and Sanofi; research funding from MSD, Novartis, Sandoz, and Sanofi; is a coordinating investigator for industry-sponsored studies for Astellas, Pharmacyclics, and Roche; and has received honoraria from Alexion, BMS, EUSA Pharma, Gilead, Jazz Pharma, Novartis, Pfizer, Roche, Sandoz, and Sanofi. AS declares consultancy for Takeda, BMS, Novartis, Janssen, MSD, Amgen, GSK, Sanofi, Kite, and Mundipharma; honoraria from Takeda, BMS, Novartis, Janssen, MSD, Amgen, GSK, Sanofi, and Kite; membership on board of directors or advisory committee for Takeda, BMS, Novartis, Janssen, Amgen, Bluebird, Sanofi, and Kite; travel expenses from Takeda, BMS, and Roche; research funding from Takeda; and participation in speakers bureaus for Takeda, BMS, Novartis, Janssen, MSD, Amgen, GSK, Sanofi, and Kite. BH declares membership on board of directors or advisory committee for ADC Therapeutics and BMS. HT declares membership on board of directors or advisory committee for ADC Therapeutics, BMS, and Roche; honoraria from Roche; and research funding from Roche. RC declares consultancy for AbbVie, Janssen, AstraZeneca, Kite, BMS, Genmab, Roche, Takeda, Kyowa Kirin, BeiGene, and Lilly; participation in speakers bureaus for AbbVie, Janssen, AstraZeneca, Kite, BMS, Roche, and Takeda; and research funding from Pfizer. DJL declares participation on advisory boards and consultancy for Janssen, Lilly, Roche, BeiGene, and Kite. MH declares participation on scientific advisory boards for AbbVie, BMS, Genmab, Janssen, Roche, and Takeda; and research support (paid to institution) from BMS, Genentech, Genmab, Incyte, Janssen, Novartis, Roche, and Takeda. MRC declares consultancy for AbbVie, Janssen, Gilead, AstraZeneca, Genmab, and Incyte; participation on advisory boards for AbbVie, Janssen, Gilead, and Genmab; and travel expenses from AbbVie, Janssen, AstraZeneca, Genmab, Roche, and Pfizer. J-MS declares consultancy or an advisory role for AbbVie, BeiGene, BMS, Gilead/Kite, Incyte, Janssen, Lilly, Miltenyi Biomedicine, Novartis, and Roche; and speaker honoraria from AbbVie, BeiGene, BMS, Gilead/Kite, Incyte, Janssen, Lilly, Novartis, and Roche. TC declares research funding from BeiGene; and participation in a speakers bureau for Janssen-Cilag. SL declares membership on board of directors or advisory committee for BeiGene, Genmab, Gilead, Incyte, Novartis, Orion, and Roche; research funding (paid to institution) from Bayer, BMS, Genmab, Hutchmed, Novartis, Nordic Nanovector, and Roche; and honoraria from Gilead, Incyte, and Novartis. MEDC declares consultancy for AbbVie, Novartis, and Sanofi; and research funding from BMS, Gilead, and Genmab. DG, YL, DH, and EF are current employees of Genmab. IA and TA are current employees of Genmab and hold stock or options in Genmab. MHD is a current employee of AbbVie. BE is a current employee of Genmab and holds patents and royalties (P158-US-PSP3). CT declares research funding from BMS, Hospira, and Roche; consultancy for AbbVie, Amgen, BMS, Cellectis, Gilead, Kite, Novartis, and Roche; honoraria from AbbVie, Amgen, Bayer, Cellectis, Gilead, Incyte, Janssen, Kite, Novartis, and Takeda; membership on board of directors or advisory committee for AbbVie, Amgen, BMS, Cellectis, Gilead, Incyte, Janssen, Kite, Novartis, Roche, and Takeda; and travel expenses from AbbVie, Amgen, BMS, Cellectis, Gilead, Kite, Novartis, and Roche. JMV declares research funding from Epizyme, Genmab, and Loxo; and consultancy for Adaptive, Genmab, and Ono. All other authors declare no competing interests.

Data sharing

De-identified individual participant data collected during the trial and additional related documents (eg, study protocol, statistical analysis plan, informed consent form) will not be made available upon request for further analyses by external independent researchers, in accordance with the data sharing policy of the sponsor based on the agreement with clinical trial sites and patients. Aggregated clinical trial data are provided via publicly accessible study registries or databases as required by law. For more information, please contact ClinicalTrials@genmab.com.

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References

1 Salles G, Schuster SJ, Fischer L, et al. A retrospective cohort study of treatment outcomes of adult patients with relapsed or refractory follicular lymphoma (ReCORD-FL). *HemaSphere* 2022; **6:** e745.

2 Ghione P, Palomba ML, Ghesquieres H, et al. Treatment patterns and outcomes in relapsed/refractory follicular lymphoma: results from the international SCHOLAR-5 study. *Haematologica* 2023; **108:** 822–32.

3 Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. *J Clin Oncol* 2015; **33:** 2516–22.

4 Casulo C, Dixon JG, Le-Rademacher J, et al. Validation of POD24 as a robust early clinical end point of poor survival in FL from 5225 patients on 13 clinical trials. *Blood* 2022; **139:** 1684–93.

5 Engelberts PJ, Hiemstra IH, de Jong B, et al. DuoBody-CD3×CD20 induces potent T-cell-mediated killing of malignant B cells in preclinical models and provides opportunities for subcutaneous dosing. *EBioMedicine* 2020; **52:** 102625.

6 van der Horst HJ, de Jonge AV, Hiemstra IH, et al. Epcoritamab induces potent anti-tumor activity against malignant B-cells from patients with DLBCL, FL and MCL, irrespective of prior CD20 monoclonal antibody treatment. *Blood Cancer J* 2021; **11:** 38.

7 Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a novel, subcutaneous CD3×CD20 bispecific T-cell-engaging antibody, in relapsed or refractory large B-cell lymphoma: dose expansion in a phase I/II trial. *J Clin Oncol* 2023; **41:** 2238–47.

8 Izutsu K, Kumode T, Yuda J, et al. Subcutaneous epcoritamab monotherapy in Japanese adults with relapsed/refractory diffuse large B-cell lymphoma. *Cancer Sci* 2023; **114:** 4643–53.

9 Hutchings M, Mous R, Clausen MR, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. *Lancet* 2021; **398:** 1157–69.

10 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.

11 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.

12 Jurczak W, Vitolo U, Linton K, et al. Patient-reported outcomes in patients with relapsed or refractory follicular lymphoma treated with epcoritamab. Annual Congress of the European Hematology Association; June 13–16, 2024 (abstr P1114).

13 Villasboas JC, Kim TM, Taszner M, et al. Results of a second, prespecified analysis of the phase 2 study ELM-2 confirm high rates of durable complete response with odronextamab in patients with relapsed/refractory (R/R) follicular lymphoma (FL) with extended follow-up. *Blood* 2023; **142** (suppl 1)**:** 3041 (abstr).

14 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:** e327–39.

15 Kim TM, Taszner M, Cho S, et al. Odronextamab in patients with relapsed/refractory (R/R) follicular lymphoma (FL) grade 1–3a: results from a prespecified analysis of the pivotal phase II study ELM-2. *Blood* 2022; **140** (suppl 1)**:** 2280–82 (abstr).

16 Budde LE, Sehn LH, Matasar M, et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. *Lancet Oncol* 2022; **23:** 1055–65.

17 Bartlett NL, Sehn LH, Matasar MJ, et al. Mosunetuzumab monotherapy demonstrates durable efficacy with a manageable safety profile in patients with relapsed/refractory follicular lymphoma who received ≥2 prior therapies: updated results from a pivotal phase II study. *Blood* 2022; **140** (suppl 1)**:** 1467–70 (abstr).

18 Schuster SJ, Sehn LH, Bartlett NL, et al. Mosunetuzumab monotherapy continues to demonstrate durable responses in patients with relapsed and/or refractory follicular lymphoma after ≥2 prior therapies: 3-year follow-up from a pivotal phase II study [oral presentation]. Annual Meeting and Exposition of the American Society of Hematology; Dec 9–12, 2023 (abstr 623).

19 Anderson KC, Landgren O, Arend RC, Chou J, Jacobs IA. Humanistic and economic impact of subcutaneous versus intravenous administration of oncology biologics. *Future Oncol* 2019; **15:** 3267–81.

20 Meyer K, Huang D, O'Day K, et al. Practice efficiency of treatment with epcoritamab versus glofitamab in relapsed/refractory diffuse large B-cell lymphoma. *Proc Am Soc Clin Oncol* 2023; **41** (suppl 16)**:** e18919 (abstr).

21 Philipp N, Kazerani M, Nicholls A, et al. T-cell exhaustion induced by continuous bispecific molecule exposure is ameliorated by treatment-free intervals. *Blood* 2022; **140:** 1104–18.

22 Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. *Nat Med* 2022; **28:** 325–32.

23 Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. *Lancet Oncol* 2022; **23:** 91–103.

24 Neelapu SS, Chavez JC, Sehgal AR, et al. Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5). *Blood* 2024; **143:** 496–506.

25 Dreyling M, Fowler NH, Dickinson M, et al. Durable response after tisagenlecleucel in adults with relapsed/refractory follicular lymphoma: ELARA trial update. *Blood* 2024; **143:** 1713–25.

26 Sabbatucci M, Vitiello A, Clemente S, et al. Omicron variant evolution on vaccines and monoclonal antibodies. *Inflammopharmacology* 2023; **31:** 1779–88.

27 WHO. WHO COVID-19 dashboard. 2024. https://data.who.int/dashboards/covid19/cases (accessed Jan 31, 2024).

28 Paszkiewicz-Kozik E, Palka M, Debowska M, et al. The outcome of the first-line therapy of patients with follicular lymphoma during COVID-19 pandemic. A real-world data from the Polish Lymphoma Research Group (PLRG). *Blood* 2023; **142** (suppl 1)**:** 1679 (abstr).

29 Langerbeins P, Hallek M. COVID-19 in patients with hematologic malignancy. *Blood* 2022; **140:** 236–52.

30 Nachar VR, Perissinotti AJ, Marini BL, Karimi YH, Phillips TJ. COVID-19 infection outcomes in patients receiving CD20 targeting T-cell engaging bispecific antibodies for B-cell non-Hodgkin lymphoma. *Ann Hematol* 2023; **102:** 2635–37.

31 García-Suárez J, de la Cruz J, Cedillo Á, et al. Impact of hematologic malignancy and type of cancer therapy on COVID-19 severity and mortality: lessons from a large population-based registry study. *J Hematol Oncol* 2020; **13:** 133.

32 Hardy N, Vegivinti CTR, Mehta M, et al. Mortality of COVID-19 in patients with hematological malignancies versus solid tumors: a systematic literature review and meta-analysis. *Clin Exp Med* 2023; **23:** 1945–59.

33 McLaughlin P, Grillo-López AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol* 1998; **16:** 2825–33.

34 Sureda Balari A, Kambhampati S, Linton K, et al. The efficacy of subcutaneous epcoritamab vs standard of care (SCHOLAR-5) in patients with relapsed/refractory follicular lymphoma after ≥2 systemic therapies: an indirect treatment comparison. Annual Congress of the European Hematology Association; June 13–16, 2024 (abstr P1140).