Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study

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Summary

Background Patients with relapsed or refractory B-cell non-Hodgkin lymphoma have few treatment options. We aimed to establish the safety and recommended phase 2 dose of epcoritamab, a novel bispecific antibody that targets CD3 and CD20 and induces T-cell-mediated cytotoxic activity against CD20+ malignant B cells.

Methods For the dose-escalation part of this phase 1/2 study, we enrolled adults (aged ≥18 years) with relapsed or refractory CD20+ B-cell non-Hodgkin lymphoma at ten sites across four countries (Denmark, the Netherlands, the UK, and Spain). Eligible patients received priming and intermediate doses followed by full doses of subcutaneous epcoritamab administered in 28-day cycles; each subsequent cohort involved escalation of the priming, intermediate, or full dose (0·0128–60 mg). The primary objectives were to determine the maximum tolerated dose and the recommended phase 2 dose. Safety, antitumour activity, pharmacokinetics, and immune biomarkers were also assessed. This study is registered with ClinicalTrials.gov, NCT03625037, with the dose-expansion part ongoing.

Findings Between June 26, 2018, and July 14, 2020, we enrolled 73 patients with relapsed, progressive, or refractory CD20+ mature B-cell non-Hodgkin lymphoma. 68 patients received escalating full doses (0·0128–60 mg) of subcutaneous epcoritamab. No dose-limiting toxic effects were observed, and the maximum tolerated dose was not reached; the full dose of 48 mg was identified as the recommended phase 2 dose. All 68 patients received at least one dose of epcoritamab and were included in safety analyses: common adverse events were pyrexia (47 patients [69%]), primarily associated with cytokine release syndrome (CRS; 40 [59%], all grade 1–2), and injection site reactions (32 [47%]; 31 grade 1). There were no grade 3 or higher CRS events. No discontinuations occurred due to treatment-related adverse events or treatment-related deaths. Overall response rate in patients with relapsed or refractory diffuse large B-cell lymphoma was 68% (95% CI 45–86), with 45% achieving a complete response at full doses of 12–60 mg. At 48 mg, the overall response rate was 88% (47–100), with 38% achieving a complete response. Patients with relapsed or refractory follicular lymphoma had an overall response rate of 90% (55–100), with 50% achieving a complete response at full doses of 0·76–48 mg. Epcoritamab induced robust and sustained B-cell depletion, and CD4+ and CD8+ T-cell activation and expansion, with modest increases in cytokine levels.

Interpretation Single-agent subcutaneous epcoritamab for treatment of patients with relapsed or refractory B-cell non-Hodgkin lymphoma merits investigation in ongoing phase 2 and phase 3 studies.

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Introduction

Despite recent advances in chemoimmunotherapy strategies, the management of relapsed or refractory B-cell non-Hodgkin lymphoma remains challenging.[1] Treatment of relapsed or refractory aggressive B-cell non-Hodgkin lymphoma in fit patients consists of high-dose chemotherapy and autologous stem-cell transplantation (ASCT).[2,3] However, at least 50% of patients relapse after ASCT.[4] Furthermore, many patients are not eligible for ASCT due to age, comorbidities, or an insufficient response to salvage chemotherapy.[5–7] Although high response rates with chemoimmunotherapy are also seen in patients with relapsed or refractory indolent B-cell non-Hodgkin lymphoma,[8] patients who relapse within 2 years after first-line therapy have a poor prognosis,[9,10] and the risk of transformation to aggressive disease remains.[11]

The paucity of safe and effective treatment options for patients with relapsed or refractory B-cell non-Hodgkin lymphoma necessitated the development of novel treatments that are well tolerated and provide deep and sustained responses to increase long-term disease-free survival and cure rates in these patients. The emergence of chimeric antigen receptor T-cell (CAR-T) therapy, which is currently available to certain patients at highly specialised treatment centres,[12] presents an important advance in the treatment of relapsed or refractory

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Research in context

Evidence before this study

We searched the PubMed database using the search terms "bispecific antibody", "CD3", "CD20", "relapsed B-cell non-Hodgkin lymphoma", and "refractory B-cell non-Hodgkin lymphoma" to identify articles published in any language from the date of database inception to March 19, 2021. In addition, we searched for these terms in published abstracts from large-scale, globally attended congresses in haematology and oncology, which included congresses sponsored by the American Society of Clinical Oncology, the American Association for Cancer Research, the American Society of Hematology, the European Society of Medical Oncology, and the European Hematology Association. We limited publications to clinical studies of single-agent therapies and excluded any conference abstracts related to epcoritamab. We identified articles and congress abstracts describing results from studies of bispecific antibodies targeting CD3 and CD20 in patients with relapsed or refractory B-cell non-Hodgkin lymphoma. Two articles described results in patients with high-risk or relapsed or refractory B-cell non-Hodgkin lymphoma who received intravenously administered anti-CD3 and anti-CD20 bispecific antibody (CD20Bi)-armed anti-CD3-activated T cells. Both studies showed that infusion of CD20Bi-armed activated T cells was safe and induced anti-lymphoma cell immunity without inhibiting engraftment. Another article described outcomes in ten paediatric patients with CD20+ B-cell lymphomas who received Lymphomun (FBTA05), administered intravenously daily (10–1000 µg) or weekly (10–50 µg). One patient with relapsed or refractory diffuse large B-cell lymphoma achieved a complete response with FBTA05 alone without donor lymphocyte infusion or chemotherapy. An article reported results from the dose-escalation part of a phase 1/2 study of glofitamab (CD20-TCB), a bispecific antibody for CD3 and CD20 administered intravenously in 171 patients with relapsed or refractory B-cell non-Hodgkin lymphoma, which included patients with diffuse large B-cell lymphoma (43%), follicular lymphoma grades 1–3A (26%), transformed follicular lymphoma (17%), or other B-cell non-Hodgkin lymphoma (15%). Across the dose range, the overall response rate was 54% (37% of patients achieved a complete response). At the recommended phase 2 dose, the overall response rate was 66% (57% complete response). Overall, 50% of patients had cytokine release syndrome (CRS; 4% of patients had grade 3 or higher CRS). Owing to the increasing frequency and severity of CRS observed with increasing dose levels, step-up dosing was subsequently introduced. At the highest fixed dose, 25 mg, all patients had CRS (grade 3 or higher CRS in 25% of patients). In the 35 patients treated with step-up dosing at the recommended phase 2 dose, 71% had CRS (grade 3 or higher CRS in 6% of patients). Congress abstracts described studies of other bispecific antibodies for CD3 and CD20 in development—odronextamab, mosunetuzumab, and plamotamab (XmAb13676)—in patients with relapsed or refractory B-cell non-Hodgkin lymphoma. In a phase 1 study of intravenous odronextamab, complete responses were observed in patients with relapsed or refractory diffuse large B-cell lymphoma and relapsed or refractory follicular lymphoma, including patients who previously received chimeric antigen receptor T-cell therapy. One patient had grade 4 CRS and seven discontinued due to treatment-related adverse events. A phase 2 study of odronextamab was initiated but subsequently paused in compliance with the US Food and Drug Administration's request for amendments to the study protocol to reduce the incidence of severe CRS. A phase 1/1b study of subcutaneous mosunetuzumab using step-up dosing showed high response rates in patients with relapsed or refractory indolent or aggressive B-cell non-Hodgkin lymphoma. The maximum tolerated dose was not reached, and one dose-limiting toxic effect (grade 4 neutropenia) was observed at a dose of 1·6 mg; grade 3 or higher CRS events were also observed. Interim results from a phase 1 study of intravenously administered plamotamab in 36 patients with relapsed or refractory diffuse large B-cell lymphoma showed seven patients achieved an objective response (two patients achieved a complete response). CRS occurred in 42% of patients (one patient had a grade 3 or higher CRS event). Although the aforementioned bispecific antibodies for CD3 and CD20 show clinical benefit in patients with relapsed or refractory B-cell non-Hodgkin lymphoma, safety concerns remain about the risk of severe CRS, and all but one require intravenous administration.

Added value of this study

Epcoritamab is a highly selective and potent bispecific antibody for CD3 and CD20 that induces T-cell-mediated cytotoxic activity against CD20+ malignant B cells. This first-in-human phase 1/2 study was initiated to evaluate subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma. The dose-escalation part of this first-in-human phase 1/2 study showed that subcutaneous epcoritamab had a manageable safety profile, notably with no grade 3 or higher CRS events, and induced robust single-agent antitumour activity in heavily pretreated patients.

Implications of all the available evidence

Subcutaneous epcoritamab was safely administered in patients with relapsed or refractory B-cell non-Hodgkin lymphoma. Step-up dosing, prophylaxis with corticosteroids, and the subcutaneous route of administration were believed to help mitigate the severity of CRS. High response rates were observed in patients with relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma. Responses were also observed in patients with mantle cell lymphoma. These results support the potential use of epcoritamab in patients with B-cell non-Hodgkin lymphoma. The clinical benefit of epcoritamab will be further validated in ongoing phase 2 and 3 trials. Given the poor prognosis of patients with relapsed or refractory B-cell non-Hodgkin lymphoma and their limited treatment options, epcoritamab shows promise as a potential novel treatment option in this population.

aggressive B-cell non-Hodgkin lymphoma. Highly specific, efficacious, targeted agents with manageable safety profiles and convenient dosing that are available off the shelf for use as single agents or in combination with currently available regimens might serve as alternative therapy options. To this end, the development of bispecific immunological agents, which target both tumour cells and T cells in patients with haematological malignancies, was initiated. Blinatumomab was the first bispecific immunotherapeutic agent targeting both CD19 on tumour cells and CD3 on T cells to be approved for a haematological malignancy and is indicated in the treatment of relapsed or refractory acute lymphoblastic leukaemia on the basis of results from a phase 2 trial.[13] As CD20 is a validated therapeutic target in B-cell malignancies, the development of bispecific antibodies that crosslink CD20 on malignant cells and CD3 on T cells was initiated.[14–16]

Epcoritamab is a full-length IgG1 bispecific antibody derived from a humanised mouse anti-human CD3 monoclonal antibody and a human anti-CD20 monoclonal antibody.[14] Epcoritamab was created via the controlled antigen-binding fragment (Fab)-arm exchange method using the DuoBody (Genmab, Utrecht, Netherlands) technology platform, which allows for retention of the native IgG1 structure and normal binding to the neonatal Fc receptor, resulting in a relatively long plasma half-life.[14] The Fc domain of epcoritamab has been modified to silence Fc-mediated effector functions, ensuring that epcoritamab does not activate T cells through Fcγ receptor-mediated CD3 crosslinking while preserving neonatal Fc receptor binding.[14]

In preclinical studies, epcoritamab induced selective, potent T-cell-mediated cytotoxic activity against CD20+ malignant B cells.[14,17] Formation of the epcoritamab–CD20–CD3 trimer leads to activation and expansion of T cells and T-cell-mediated killing of CD20+ malignant B cells, thus differentiating epcoritamab from conventional CD20 monoclonal antibodies that induce T-cell cytotoxicity through Fc-mediated effector functions.[14] Compared with three other bispecific antibody analogue constructs that target CD3 and CD20, epcoritamab showed significantly higher potency at lower doses in vitro; effective concentrations at half-maximal cytotoxic activity against B-cell lymphoma cell lines and endogenous B cells ranged from 0·2 pM to 3·5 pM.[14] Notably, this finding translated into epcoritamab retaining its antitumour activity in vivo in the presence of a rituximab analogue.[14] Subcutaneous administration of epcoritamab is supported by an in-vivo study in cynomolgus monkeys, which showed a similar degree of prolonged B-cell depletion with subcutaneous and intravenous administration.[14] Importantly, subcutaneous administration also resulted in delayed and lower peak cytokine levels than intravenous administration,[14] suggesting that the subcutaneous route of administration could potentially reduce the risk of severe cytokine release syndrome (CRS). Epcoritamab also showed cytotoxic activity in malignant B cells isolated from patients with B-cell non-Hodgkin lymphoma who were previously treated with CD20 antibodies as well as in those from newly diagnosed patients.[17]

Overall, these findings led to the initiation of a first-in-human phase 1/2 dose-escalation and expansion trial of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma. We report findings from the phase 1 dose-escalation part of this ongoing study, where the primary objectives were to establish the maximum tolerated dose and the recommended phase 2 dose.

Methods

Study design and participants

This first-in-human, multicentre, open-label, phase 1/2 trial was initiated on June 26, 2018, and consisted of dose-escalation and dose-expansion parts. Patients enrolled at ten sites across four countries (Denmark, the Netherlands, the UK, and Spain; appendix p 2) were assigned to subcutaneous epcoritamab injections with predefined step-up and target doses.

See Online for appendix

The study population for the dose-escalation part consisted of adults (aged 18 years and older) with relapsed, progressive, or refractory CD20+ mature B-cell non-Hodgkin lymphoma (including patients with de-novo or transformed diffuse large B-cell lymphoma, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, small lymphocytic lymphoma, and marginal zone lymphoma).[18] Demonstration of CD20 positivity on the basis of local pathological evaluation was required; however, the method or threshold to verify CD20 positivity was not specified. Eligible patients were required to have received previous treatment with an anti-CD20 monoclonal antibody-containing regimen and be ineligible to receive all standard therapeutic options. Patients were required to have measurable disease, an Eastern Cooperative Oncology Group performance status of 0–2, and adequate renal and hepatic function. Patients were excluded if they had CNS lymphoma (or known CNS involvement), received CAR-T therapy within 30 days before the first dose of epcoritamab, had chronic or ongoing infections, or required immunosuppressive therapy. Patients who received previous allogeneic stem-cell transplantation (SCT) or solid organ transplantation were excluded (appendix p 3). All patients reviewed and signed informed consent forms before enrolling in the study. The study was done in accordance with the guidelines on good clinical practice put forth by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the principles of the Declaration of Helsinki. Approval by site-specific institutional review boards or institutional ethics committees was obtained before study initiation (appendix p 2).

Procedures

In the phase 1 dose-escalation part of the study, patients received subcutaneous epcoritamab using a step-up approach, which entailed administration of predefined priming or intermediate doses over a 2-week period, followed by full doses ranging from 0·0128 mg to 60 mg by cohort (appendix p 11). The step-up dosing approach was intended to mitigate the severity of CRS. Patients received the priming dose of subcutaneous epcoritamab on day 1 of cycle 1 and an intermediate dose (introduced at the 1·5 mg full dose level to bridge the widening gap between the priming dose and the full dose) on day 8 of cycle 1. Subcutaneous epcoritamab (1 mL) was administered in 28-day cycles until disease progression or unacceptable toxicity, according to the following schedule: weekly dosing in cycles 1 and 2 (days 1, 8, 15, 22), dosing every 2 weeks in cycles 3–6 (days 1, 15), and dosing every 4 weeks from cycle 7 onward (day 1). Prophylactic treatment with corticosteroids (prednisolone 100 mg or equivalent), antipyretics (oral paracetamol 650–1000 mg or equivalent), and antihistamines (diphenhydramine 50 mg or equivalent) was administered 30–120 min before the first four subcutaneous epcoritamab injections (during cycle 1) and as needed during cycle 2 as an additional measure to mitigate CRS severity. As a further precaution, patients were hospitalised for at least 72 h after the first and second administrations of epcoritamab and for 24 h after the third and fourth administrations of epcoritamab (during cycle 1). The specific doses of epcoritamab by cohort in cycle 1 are presented in the appendix (p 5).

Dose escalation was done using a modified Bayesian optimal interval design, which provided greater flexibility than the standard 3+3 design (appendix p 10).[19] In this trial, the target rate for dose-limiting toxic effects was set at 30% with a boundary for dose escalation of 23·6% and a boundary for dose de-escalation of 35·9%. The modification of Bayesian optimal interval escalation and de-escalation rules includes exemptions in the case of six or nine patients evaluable for dose-limiting toxic effects, and use of both accelerated and standard titration parts.

The decision to escalate to the next highest dose was made by comparing the observed rate of dose-limiting toxic effects with the two predetermined fixed boundaries (23·6% and 35·9%), with the target rate of dose-limiting toxic effects of 30% falling between the two boundaries. Details related to dose-escalation stopping criteria are outlined in the appendix (pp 1–2). The evaluation period for dose-limiting toxicity spanned the first 4 weeks (ie, 28 days) after the first administration of subcutaneous epcoritamab. No dose modifications were allowed during the study, but dose interruptions were permitted. A patient who experienced a dose-limiting toxic effect could continue epcoritamab therapy if the severity of the dose-limiting toxicity decreased to at most grade 2 or baseline within 4 weeks. The Data Monitoring Committee reviewed all available data and evaluated newly emergent safety data including dose-limiting toxicity and provided the Sponsor Safety Committee with recommendations for the next dose level.

Patients could receive concomitant medications or treatments for the purpose of receiving adequate care as clinically indicated, including supportive care for the management of CRS (saline infusion; systemic glucocorticosteroid, antihistamine, or antipyretic medications; vasopressin or vasopressors; low-flow or high-flow oxygen or positive-pressure ventilation support; or intravenous tocilizumab), supportive therapy for tumour lysis syndrome (including rasburicase), and prophylactic antibiotic, antiviral, or antifungal therapy for patients at increased risk for or with a history of infections. The use of granulocyte colony-stimulating factor for neutropenia and blood transfusions was also permitted.

Outcomes

The primary endpoints of the dose-escalation part of this first-in-human trial were the maximum tolerated dose and the recommended phase 2 dose of epcoritamab. Treatment-emergent adverse events were evaluated and graded according to Common Terminology Criteria for Adverse Events (version 4.03). CRS was graded according to consensus criteria from the American Society for Transplantation and Cellular Therapy.[20] Clinical tumour lysis syndrome was graded according to Cairo-Bishop criteria.[21] Additional endpoints were antitumour activity or treatment response, progression-free survival, and pharmacokinetic parameters; pharmacodynamic and treatment response biomarkers were also evaluated.

Efficacy assessments consisted of radiographic disease evaluation for treatment response every 6 weeks for the first 24 weeks (±3 weeks), and every 24 weeks (±12 weeks) thereafter. Radiographic assessments consisted of fluorodeoxyglucose (FDG)-PET-CT scans or FDG-PET with CT or MRI when combined PET-CT scans were not available. PET scans were not initially required for disease evaluation but were later implemented after a protocol amendment (Nov 4, 2019). Treatment responses during dose escalation were evaluated on the basis of Lugano classification response criteria[22,23] by the site investigator. Progression-free survival was defined as the time from day 1 of cycle 1 to first documented disease progression or death due to any cause, whichever occurred earlier. Patients who remained alive without disease progression at the date of clinical cutoff were censored at the date of last disease assessment before the start of subsequent anti-lymphoma therapy. For patients who remained alive without a post-baseline tumour assessment, progression-free survival was censored on the first dosing date. Pharmacokinetic analyses of epcoritamab were done in blood samples obtained at prespecified timepoints (appendix p 6).

An integrated semi-mechanistic pharmacokinetic and pharmacodynamic modelling approach, which incorporated preclinical pharmacokinetic and pharmacodynamic data from cynomolgus monkeys as well as

clinical pharmacokinetic, biomarker, exposure–response, and exposure–safety analyses from this study, was used to establish the recommended phase 2 dose. The model was calibrated using clinical exposure–response data and was then used to simulate diffuse large B-cell lymphoma and follicular lymphoma on the basis of differences in tumour growth rates to predict trimer formation (appendix p 1).

An exploratory analysis of potential biomarkers associated with clinical response to epcoritamab was done using peripheral blood samples obtained at screening and during treatment to evaluate the effects of treatment on circulating immune cells (appendix p 6). Whole-blood flow cytometry was used to detect immune cells, and ELISAs were used to detect plasma cytokine concentrations.

Statistical analysis

A sample size of 70 patients was considered adequate for the dose-escalation study and provided a sufficient basis for the design of the phase 2 expansion part of this study and subsequent trials. The selected sample size allowed for implementation of the modified Bayesian optimal interval design for dose escalation (appendix p 10). No formal sample size calculations or statistical hypotheses were implemented in the dose-escalation part of this study. Categorical data were summarised and presented as frequencies and percentages. Continuous data were summarised by the number of non-missing values and presented as mean (SD) and median (IQR). No imputation of missing data was done for the safety and pharmacokinetic endpoints. Time-to-event parameters were described using Kaplan-Meier estimates (median time and IQR with approximate 95% CIs). Median progression-free survival was estimated using the Kaplan-Meier method and reported with 95% CIs derived using the Brookmeyer and Crowley method with logarithmic transformation. Safety analyses were done on the safety analysis set, which was the same as the full analysis population and consisted of all patients who received at least one dose of epcoritamab. Treatment response was evaluated in the modified response-evaluable population, which consisted of all patients in the full analysis population who had measurable disease at baseline and at least one post-baseline disease assessment. The dose-determining analysis population consisted of all patients in the full analysis population who either met the minimum exposure criterion (ie, had received at least 90% of the planned dose in the first three administrations of epcoritamab) and completed the dose-limiting toxicity evaluation period with sufficient safety evaluations or had a dose-limiting toxic effect during the dose-limiting toxicity evaluation period. The dose-determining analysis population was used in the analysis of the maximum tolerated dose.

The trial was monitored by the study sponsor. Data were obtained using electronic data capture. Trial-site personnel transcribed the data from source documents onto electronic case report forms, which were securely transferred to the study sponsor. All source documents, electronic case report forms, and other required documents were maintained in compliance with ICH good clinical practice guidelines. Data were analysed using SAS software (version 9.4). This trial is registered at ClinicalTrials.gov, NCT03625037.

Role of the funding source

This study was funded by Genmab and AbbVie. Epcoritamab is being jointly developed by Genmab and AbbVie. The sponsor was involved with data collection, analysis, interpretation, writing of the manuscript, and the decision to submit for publication.

Results

The first patient was enrolled on June 26, 2018, and the last patient was enrolled on July 14, 2020. 73 patients were enrolled in the dose-escalation part and 68 received epcoritamab at full doses of 24 mg or less (n=53), 48 mg (n=12), or 60 mg (n=3; figure 1; table 1). Of the 68 patients, 46 (68%) had diffuse large B-cell lymphoma, 12 (18%) had follicular lymphoma, four (6%) had mantle cell lymphoma, and three (4%) had high-grade B-cell lymphoma; the remaining three patients had primary mediastinal large B-cell lymphoma, small lymphocytic lymphoma, and marginal zone lymphoma based on WHO classification criteria.[18] Most patients (94%) had an Eastern Cooperative Oncology Group performance status of 0–1, all were refractory to or had relapsed after treatment with anti-CD20

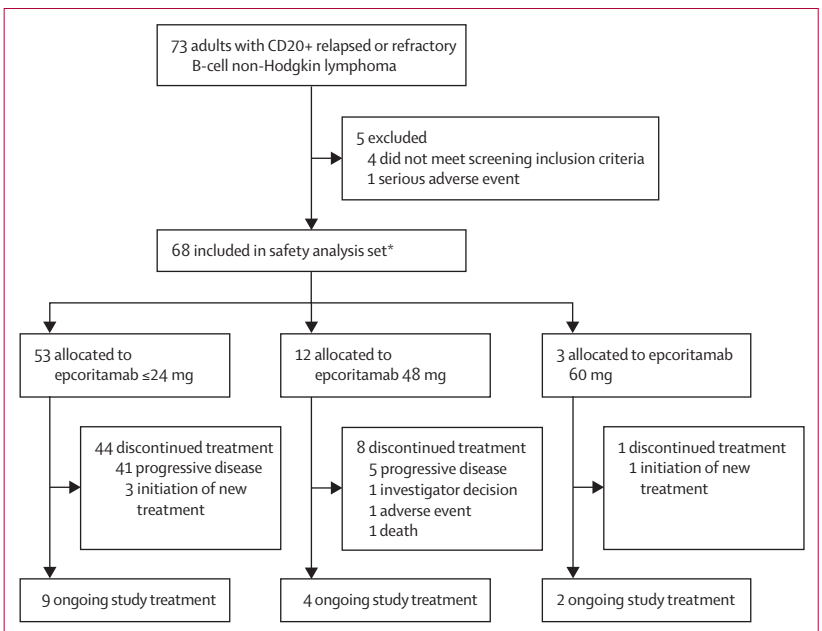

Figure 1: **Trial profile**
*All patients who received at least one dose of epcoritamab.

	Relapsed or refractory diffuse large B-cell lymphoma (n=46)	Relapsed or refractory follicular lymphoma (n=12)	All patients (n=68)*
Age, years	68 (55–74)	73 (63–76)	68 (57–75)
Sex			
Female	16 (35%)	4 (33%)	23 (34%)
Male	30 (65%)	8 (67%)	45 (66%)
ECOG performance status			
0	23 (50%)	6 (50%)	35 (51%)
1	21 (46%)	4 (33%)	29 (43%)
2	2 (4%)	1 (8%)	3 (4%)
3†	0	1 (8%)†	1 (1%)†
Ann Arbor stage			
I	3 (7%)	0	3 (4%)
II	5 (11%)	4 (33%)	12 (18%)
III	12 (26%)	4 (33%)	16 (24%)
IV	26 (57%)	4 (33%)	37 (54%)
Extranodal disease	29 (63%)	6 (50%)	42 (62%)
Time since diagnosis, months	25·4 (11·0–54·6)	61·5 (34·3–153·1)	29·7 (13·7–66·8)
Time since relapse or progression, months	1·5 (1·1–2·3)	1·6 (1·2–2·6)	1·6 (1·1–2·3)
Number of lines of previous therapy	3·0 (2·0–4·0)	4·5 (2·5–8·0)	3·0 (2·0–4·5)
Previous therapies			
Anti-CD20 monoclonal antibody	46 (100%)	12 (100%)	68 (100%)
Anthracyclines	46 (100%)	9 (75%)	62 (91%)
Alkylating agents	46 (100%)	12 (100%)	67 (99%)
Autologous stem-cell transplantation	7 (15%)	1 (8%)	10 (15%)
CAR-T therapy	5 (11%)	0	6 (9%)
Treatment-refractory patients by therapy			
Last line of systemic therapy	41 (89%)	10 (83%)	58 (85%)
Alkylating agents	40 (87%)	9 (75%)	56 (82%)
Last anti-CD20 monoclonal antibody	41 (89%)	10 (83%)	59 (87%)

Data are median (IQR) or n (%). CAR-T=chimeric antigen receptor T-cell. ECOG=Eastern Cooperative Oncology Group. *Ten patients had other B-cell non-Hodgkin lymphoma histologies, including mantle cell lymphoma (n=4), high-grade B-cell lymphoma (n=3), primary mediastinal B-cell lymphoma (n=1), small lymphocytic leukaemia (n=1), and marginal zone lymphoma (n=1). †During the screening period, one patient with follicular lymphoma had an ECOG performance status of 2 and met the inclusion criteria; however, before dosing on day 1 of cycle 1, the patient was found to have an ECOG performance status of 3; on the basis of the full analysis principle, this patient was included in the study.

Table 1: **Baseline characteristics**

	Grade 1–2	Grade 3	Grade 4
Pyrexia*	43 (63%)	4 (6%)	0
Cytokine release syndrome	40 (59%)	0	0
Injection site reaction	32 (47%)	0	0
Fatigue	26 (38%)	4 (6%)	0
Diarrhoea	18 (26%)	0	0
Hypotension*	17 (25%)	4 (6%)	0
Dyspnoea	16 (24%)	0	1 (1%)
Tachycardia*	14 (21%)	0	0
Anaemia	7 (10%)	9 (13%)	0

*Most pyrexia, hypotension, and tachycardia events were associated with cytokine release syndrome.

Table 2: **Treatment-emergent adverse events that occurred in at least 20% of the full analysis population (n=68)**

monoclonal antibodies, and almost all (99%) had received previous chemotherapy. The patients had received a median of three previous lines of therapy and most (58 [85%] of 68 patients) were refractory to their last line of systemic therapy. Six (9%) patients had received previous CAR-T therapy. Patients with diffuse large B-cell lymphoma (n=46) had received a median of three previous lines of systemic therapy; seven (15%) patients had received previous ASCT and five (11%) had received previous CAR-T therapy. Patients with follicular lymphoma (n=12) had received a median of five lines of previous systemic therapy.

As of the data cutoff date of Jan 31, 2021, 15 (22%) of 68 patients remained on treatment with epcoritamab. The most common reason for discontinuation of the study treatment was progressive disease (46 [68%] of 68 patients). One patient discontinued treatment because of an unrelated fatal adverse event (COVID-19 pneumonia). No patients discontinued because of treatment-related adverse events.

Median duration of exposure to epcoritamab in the 24 mg or less, 48 mg, and 60 mg dose groups was 8·1 weeks (IQR 4·1–24·1), 11·8 weeks (5·8–30·6), and 40·1 weeks (11·0–40·3), respectively. No dose-limiting toxic effects or dose reductions occurred during the dose-limiting toxicity evaluation period and the maximum tolerated dose was not reached up to the highest dose of 60 mg. The most common treatment-emergent adverse events were pyrexia (47 [69%] of 68 patients), primarily associated with CRS (40 [59%] of 68), and injection site reactions (32 [47%] of 68; tenderness, warmth, erythema, itching, and pain; table 2). Most incidences of pyrexia (43 [91%] of 47) were of grade 1 or 2 severity and all but one injection site reaction (31 [97%] of 32) were of grade 1 severity. Serious adverse events were reported in 46 (68%) patients, the most common being pyrexia and pneumonia; pyrexia was the only serious treatment-related adverse event occurring in at least 5% of patients (19 [28%] of 68). There were no cases of febrile neutropenia. All serious adverse events (appendix p 7), grade 3 or 4 treatment-emergent adverse events (appendix p 8), and fatal adverse events (appendix p 9) are listed in the appendix.

Adverse events of special interest—specifically CRS, neurological events, and clinical tumour lysis syndrome—are shown in table 3. CRS was observed in all dose groups; all CRS events were grade 1–2 and were manageable using local institutional protocols, without the need for intensive care unit hospitalisation. Most CRS events occurred during cycle 1. The median time to onset of the first CRS event after the first priming dose was 1·4 days (IQR 0·9–3·1) and, after the first full dose, it was 1·8 days (0·8–3·1). The incidence or severity of CRS did not increase at higher full doses of epcoritamab. The median

time to resolution of the longest CRS event was 1·0 day (0·5–2·0) for events occurring after the first priming dose and 2·2 days (0·9–4·6) for events occurring after the first full dose. All patients who had CRS recovered without the need for vasopressor therapy or high-flow oxygen. In the 48 mg full-dose cohort, no CRS events were reported after the second full dose or subsequent doses. The most frequent symptoms of CRS were pyrexia (40 [59%] of 68 patients), hypotension (16 [24%]), hypoxia (12 [18%]), tachycardia (ten [15%]), and chills (seven [10%]). Neurological symptoms possibly related to epcoritamab were reported in four patients who received doses of 24 mg or lower (grade 1 partial seizure, grade 1 agraphia, grade 3 hypersomnia, and grade 3 confusion and depressed level of consciousness); all were transient (median duration 3·0 days [2·5–6·0]) and patients recovered without sequelae. Grade 3 clinical tumour lysis syndrome was observed in a patient with primary mediastinal large B-cell lymphoma in the setting of retroperitoneal haemorrhage related to progression of bulky disease.

11 of 68 patients died on treatment (all due to disease progression). Overall, including survival follow-up, 38 (56%) of 68 patients died, and disease progression was the most common cause of death (33 [49%]). Other causes of death, all post treatment, were COVID-19 (n=1), lymphoma (n=1), graft-versus-host disease (n=1), and septic shock (n=1); the cause of death was unknown in one patient. No deaths occurred due to treatment-related adverse events.

Epcoritamab showed a dose-dependent exposure profile, with a mean half-life of 8·8 days following administration of the first full dose; the mean time to reach maximum plasma concentration was 2·8 days. Based on the simulated pharmacokinetic and pharmacodynamic model, response rates started to plateau at the 48 mg epcoritamab dose for patients with diffuse large B-cell lymphoma and those with follicular lymphoma, which was in line with predicted epcoritamab–CD3–CD20 trimer formation (figure 2). Increasing the dose beyond 48 mg did not provide any substantial increase in the predicted response rate. Simulation done with the fitted pharmacokinetic model to assess pharmacokinetic dose proportionality also showed that saturation of non-linearity in the pharmacokinetics occurs at epcoritamab doses of 48 mg and higher (appendix p 12). On the basis of a clinical trial simulation using the pharmacokinetic and pharmacodynamic model, exposure–response and exposure–safety analyses, and safety data, 48 mg was identified as the recommended phase 2 dose as well as the lowest biologically effective dose, which was associated with optimal trimer formation and improved clinically relevant response rates, while potentially minimising safety risks.

Antitumour responses were observed in patients with relapsed or refractory diffuse large B-cell lymphoma (0·76 mg to <12 mg: 13% overall response rate [95% CI 2–38], 13% complete response [2–38]; 12 mg to 60 mg: 68% overall response rate [45–86], 45% complete response [24–68]; 48 mg: 88% overall response rate [47–100], 38% complete response [9–76]; 48 mg to 60 mg: 91% overall response rate [59–100], 55% complete response [23–83]; table 4; figure 3A). Response data for patients with relapsed or refractory diffuse large B-cell lymphoma are presented at the recommended phase 2 dose (48 mg) and doses of 12 mg or higher, doses associated with saturation of target engagement. In patients with relapsed or refractory diffuse large B-cell lymphoma who received doses of 12 mg or higher, the median time to response was 1·4 months (IQR 1·3–2·6); median time to reach complete response was 2·7 months (1·3–2·8). Treatment response deepened over time, with five patients initially achieving a partial response at week 6 that subsequently converted to a complete response; the time to conversion ranged from 5·4 weeks to 11·1 weeks. The estimated probability of diffuse large B-cell lymphoma responders (all dose groups) maintaining remission for at least 6 months was 75% (95% CI 46–90). Six of the ten patients with a response at doses of 48 mg or higher had an ongoing response at the time of data cutoff, with five of these patients achieving a complete response (figure 3B). Among the ten patients with relapsed or refractory diffuse large B-cell lymphoma who achieved a complete response after receiving doses of 12 mg or higher (median follow-up 9·2 months [IQR 7·4–14·8]), all were in remission at last assessment during treatment with epcoritamab. The longest duration of ongoing complete response was more than 11·2 months. Three patients with diffuse large B-cell lymphoma who achieved a complete response went on to receive SCT (one received ASCT and two received allogeneic SCT) with curative intent (figure 3B). One of the three patients who underwent transplantation was alive and in remission at the time of data cutoff; causes of death in the two remaining patients were septic shock and graft-versus-host disease. The median duration of follow-up for patients with relapsed or refractory diffuse large B-cell lymphoma who received previous CAR-T therapy was

	Epcoritamab dose			Total (n=68)
	≤24 mg (n=53)	48 mg (n=12)	60 mg (n=3)	
Cytokine release syndrome				
Total	30 (57%)	8 (67%)	2 (67%)	40 (59%)
Grade 1	15 (28%)	4 (33%)	1 (33%)	20 (29%)
Grade 2	15 (28%)	4 (33%)	1 (33%)	20 (29%)
Neurological symptoms				
Total	4 (8%)	0	0	4 (6%)
Grade 1	2 (4%)	0	0	2 (3%)
Grade 3	2 (4%)	0	0	2 (3%)
Clinical tumour lysis syndrome				
Total	0	1 (8%)	0	1 (1%)
Grade 3	0	1 (8%)	0	1 (1%)

Table 3: **Adverse events of special interest in the full analysis population (n=68)**

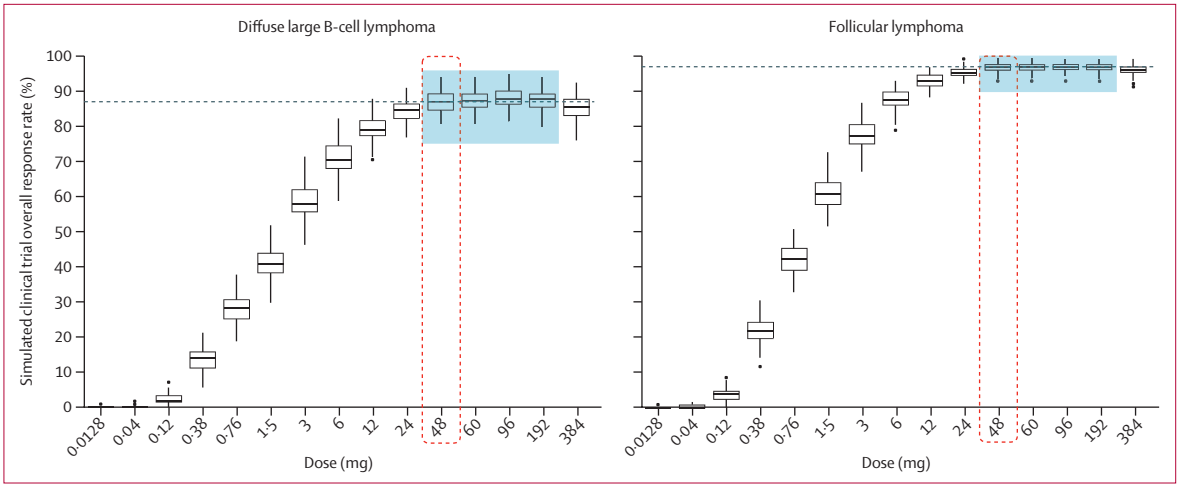

***Figure 2*: Simulated exposure of epcoritamab**

Clinical trial simulation was done using the calibrated pharmacokinetic and pharmacodynamic model. At each dose, 100 trials were simulated. The box plot summarises the response rates from 100 simulated trials. In each trial, simulations were done for 128 patients and the overall response rate of each simulated trial was calculated on the basis of change in tumour size for each simulated patient. Simulations for diffuse large B-cell lymphoma and follicular lymphoma were differentiated on the basis of differences in tumour doubling times reported in the literature (around 1 month for diffuse large B-cell lymphoma and around 6 months for follicular lymphoma).

	Relapsed or refractory diffuse large B-cell lymphoma*			Relapsed or refractory follicular lymphoma†		Relapsed or refractory mantle cell lymphoma‡	
	12–60 mg (n=22)	48 mg (n=8)	60 mg (n=3)	0·76–48 mg (n=10)	48 mg (n=1)	0·76–48 mg (n=4)§	48 mg (n=1)
Overall response, n (%, 95% CI)	15 (68%, 45–86)	7 (88%, 47–100)	3 (100%, 29–100)	9 (90%, 55–100)	0 (0, 0–98)	2 (50%, 7–93)	1 (100%, 3–100)
Complete response	10 (45%)	3 (38%)	3 (100%)	5 (50%)	0	1 (25%)	0
Partial response	5 (23%)	4 (50%)	0	4 (40%)	0	1 (25%)	1 (100%)
Stable disease	1 (5%)	0	0	0	0	1 (25%)	0
Progressive disease	5 (23%)	0	0	1 (10%)	1 (100%)	0	0
Time to response, months	1·4 (1·3–2·6)	1·4 (1·3–2·6)	1·3 (1·1–1·4)	1·9 (1·5–3·5)	NA	1·4 (1·3–1·5)	1·3 (1·3–1·3)
Follow-up duration, months	9·3 (8·2–14·8)	8·2 (7·4–9·9)	9·2 (9·2–9·3)	13·6 (10·4–16·5)	6·6 (6·6–6·6)	10·2 (7·7–10·5)	7·7 (7·7–7·7)

Data are n (%) or median (IQR), unless otherwise stated. Response assessments were based on Lugano classification response criteria[22,23] by investigator assessment. The modified response-evaluable population (defined as patients with at least one post-baseline disease assessment or who died without a post-baseline disease assessment) excluded one patient with relapsed or refractory diffuse large B-cell lymphoma who discontinued before first assessment due to COVID-19 pneumonia and one patient with relapsed or refractory follicular lymphoma who discontinued before first assessment due to coronary artery bypass surgery. Data are not shown for 23 patients with relapsed or refractory diffuse large B-cell lymphoma who received doses of less than 12 mg or for six additional patients with other relapsed or refractory B-cell non-Hodgkin lymphoma histologies. One patient with diffuse large B-cell lymphoma did not receive a full dose of epcoritamab; the patient died of COVID-19 and was not response-evaluable. NA=not applicable. *Includes three patients who received the 60 mg dose before the recommended phase 2 dose was established. †PET scan was not mandatory until a protocol amendment on Nov 4, 2019. ‡Three patients had blastoid or pleomorphic mantle cell lymphoma; one had unknown histology. §Includes one patient who died before response assessment.

***Table 4:* Treatment response by diagnosis in the modified response-evaluable set (n=66)**

5·8 months (1·0–7·0). All four evaluable patients with diffuse large B-cell lymphoma who had previously received CAR-T therapy (one with relapsed diffuse large B-cell lymphoma and three with refractory diffuse large B-cell lymphoma) responded to treatment (two [50%] had a complete response and two [50%] had a partial response; figure 3B); two of these patients proceeded to SCT. Median progression-free survival for patients with relapsed or refractory diffuse large B-cell lymphoma who received doses of epcoritamab of at least 12 mg was 9·1 months (IQR 1·6–not estimable); median progression-free survival for patients who received doses of at least 48 mg has not been reached (figure 3C).

For assessment of antitumour activity in patients with relapsed or refractory follicular lymphoma, a dose threshold of 0·76 mg or higher was chosen on the basis of the minimal efficacy threshold and pharmacokinetic and pharmacodynamic modelling. High response rates

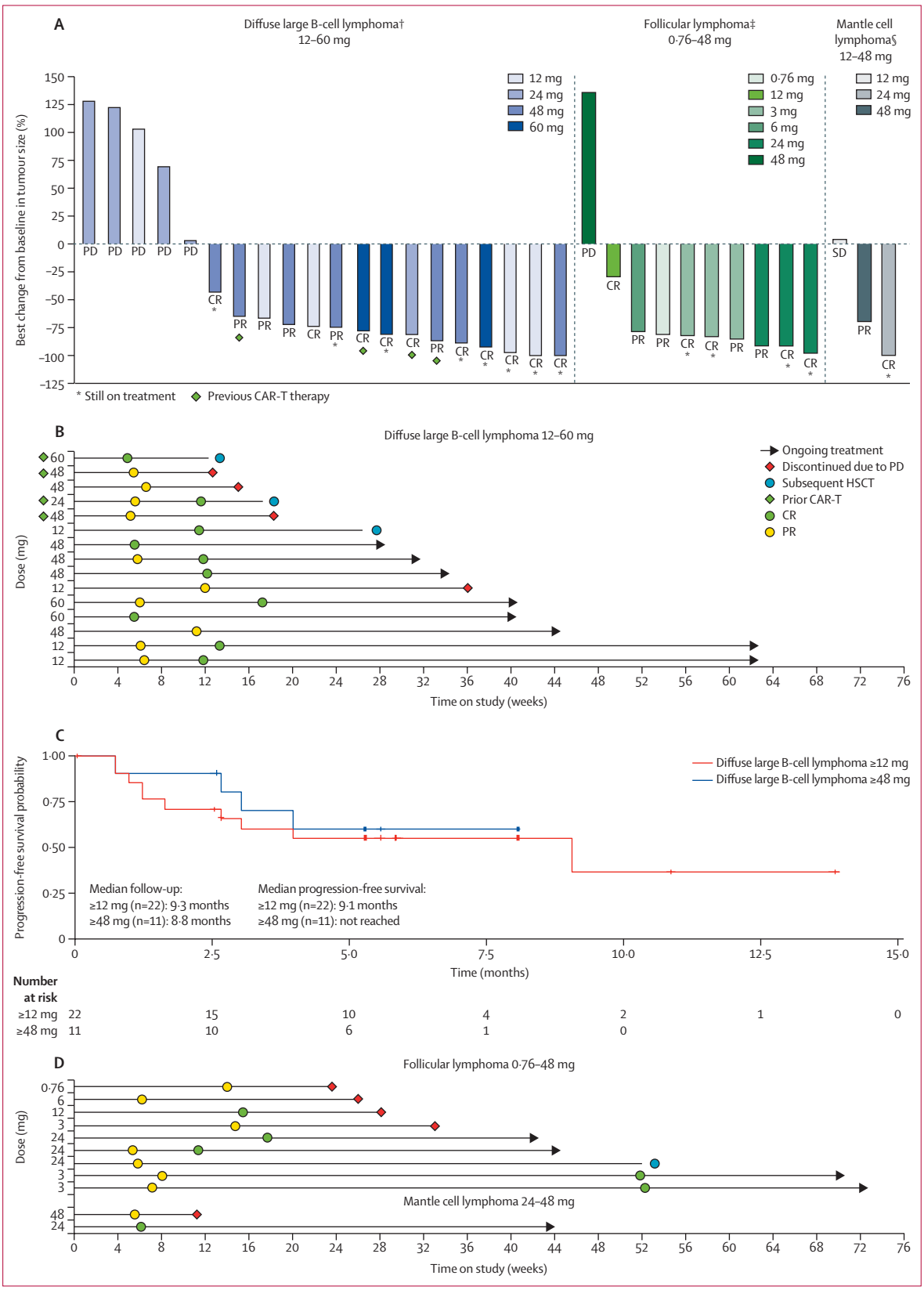

***Figure 3*: Treatment response in patients with relapsed or refractory diffuse large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma**

(A) Best percent change from baseline in tumour size in patients with diffuse large B-cell lymphoma who received epcoritamab 12–60 mg (n=22†), patients with follicular lymphoma who received epcoritamab 0·76–48 mg (n=10‡), and patients with mantle cell lymphoma who received epcoritamab 12–48 mg (n=4§; modified response-evaluable population). (B) Response profile in patients with relapsed or refractory diffuse large B-cell lymphoma. (C) Progression-free survival in patients with relapsed or refractory diffuse large B-cell lymphoma at epcoritamab doses of 12–60 mg. Perpendicular dashes denote censored data. (D) Response profiles in patients with relapsed or refractory follicular lymphoma or mantle cell lymphoma. Data are shown for the modified response-evaluable population, which excluded one patient with COVID-19 pneumonia and one patient who discontinued before first assessment because of coronary artery bypass surgery. A PET scan was not initially required for follicular lymphoma; protocol amendment added PET follow-up of all FDG-avid disease. CAR-T=chimeric antigen receptor T-cell. CR=complete response. FDG=fluorodeoxyglucose. HSCT=haematopoietic stem-cell transplantation. PD=progressive disease. PR=partial response. SD=stable disease. †Excludes two patients with diffuse large B-cell lymphoma; one patient died before receiving the first post-baseline evaluation and one patient did not have measurable disease based on CT scan evaluation at the time of enrolment. ‡Modified response-evaluable population. §Excludes one patient with mantle cell lymphoma who died before post-baseline assessment.

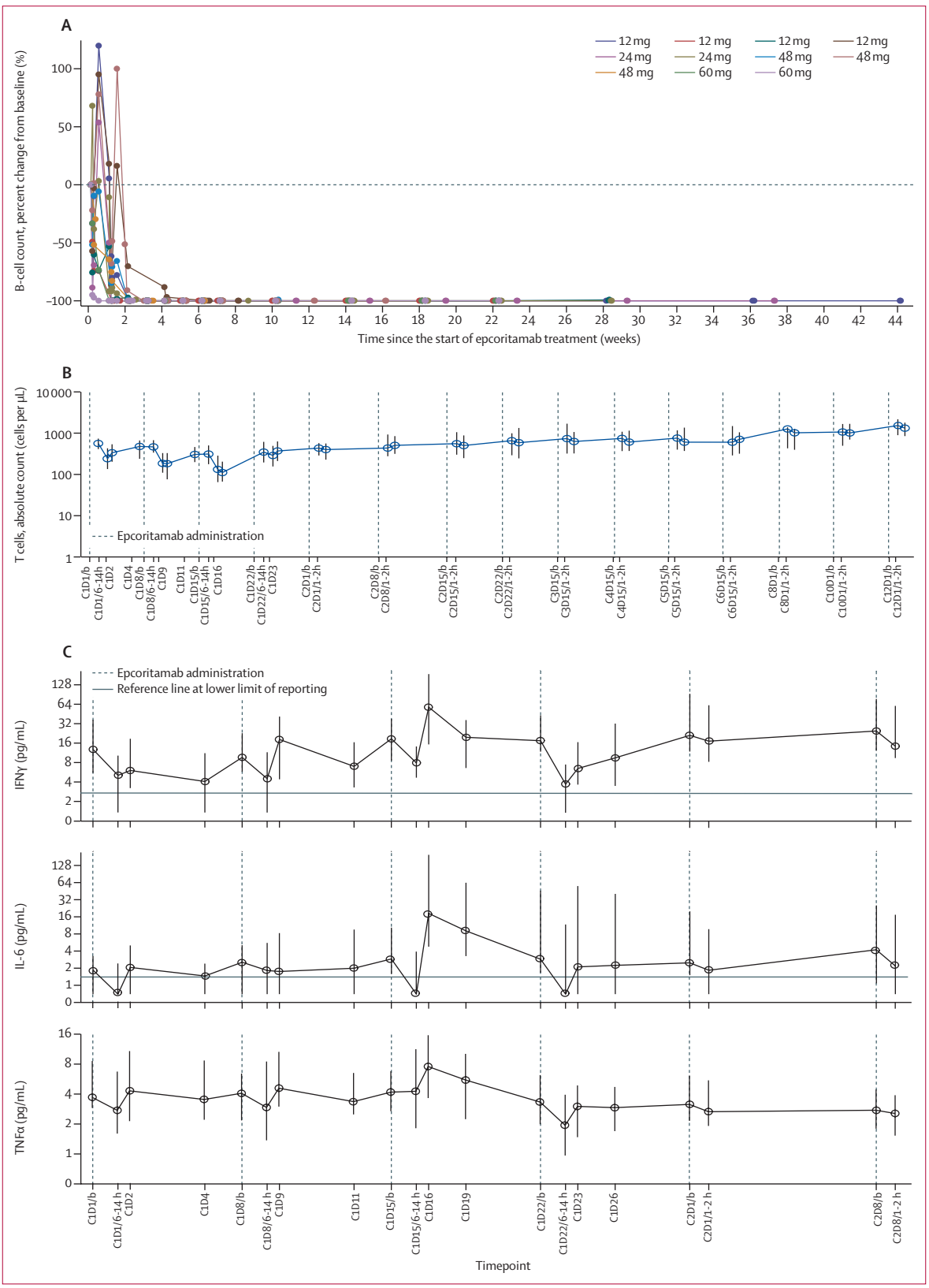

***Figure 4*: Changes in immune cell populations and cytokine levels in patients treated with epcoritamab**
(A) Change in peripheral B-cell concentrations over time after treatment with subcutaneous epcoritamab (coloured lines represent individual patients). (B) T-cell expansion in peripheral blood after administration of subcutaneous epcoritamab (all patients received epcoritamab dose ≥12 mg). Y-axis is on a log10 scale. (C) Longitudinal change in median cytokine levels after administration of subcutaneous epcoritamab (IFNγ: all patients ≥12 mg epcoritamab; IL-6: all patients ≥12 mg epcoritamab; TNFα: patients with diffuse large B-cell lymphoma ≥12 mg epcoritamab). Y-axes are on a log2 scale. Median values are shown; error bars represent the IQR. b=baseline. C=cycle. D=day. IFNγ=interferon γ. IL-6=interleukin 6. log=logarithm. TNFα=tumour necrosis factor α.

were observed in the ten evaluable patients with relapsed or refractory follicular lymphoma treated with doses of 0·76 mg or higher (90% overall response rate, 50% complete response; table 4). The median time to response was 1·9 months (IQR 1·5–3·5). Notably, PET scans were not done in some patients with relapsed or refractory follicular lymphoma as these were not initially mandatory according to the protocol; in the absence of PET, CT scans might have failed to detect a complete metabolic response. In five evaluable patients treated with full doses of 12–48 mg epcoritamab, the overall response rate was 80% (95% CI 28–99) and the complete response rate was 60% (15–95). Responses deepened over time in three patients with relapsed or refractory follicular lymphoma in whom an initial partial response converted to complete response over a period of 6–45 weeks; five patients had an ongoing response at the time of data cutoff (figure 3D). Data related to progression-free survival in patients with relapsed or refractory follicular lymphoma were immature at the time of data cutoff.

Responses were observed in two of the four evaluable patients with relapsed or refractory mantle cell lymphoma (0·76–48 mg: 50% overall response rate, 25% complete response, 25% partial response; table 4, figure 3D), and both patients had the blastoid or pleomorphic variant of mantle cell lymphoma. Median time to response was 1·4 months (IQR 1·3–1·5). Of the three patients with high-grade B-cell lymphoma, one who received full doses of 6 mg achieved a partial response; of the remaining two patients, one had stable disease after receiving the 6 mg full dose and one had progressive disease after receiving the 0·12 mg full dose.

In patients with detectable B cells at baseline, epcoritamab induced a rapid, profound, and sustained depletion of circulating peripheral B cells and a gradual increase in peripheral T cells at doses ranging from 0·76 mg to 48 mg (figures 4A, B). A transient decrease in circulating peripheral CD4+ T cells and CD56– and CD8+ T cells was observed within 6 h of the first subcutaneous dose of epcoritamab; subsequent dosing elicited expansion of CD4+ and CD8+ T cells after 6–8 weeks of treatment (appendix p 13). Step-up dosing with subcutaneous epcoritamab was associated with moderate increases in interferon γ, interleukin 6, and tumour necrosis factor α (figure 4C).

Discussion

Despite recent advances in the treatment of relapsed or refractory B-cell non-Hodgkin lymphoma, there is an unmet need for novel therapeutics that are safe, efficacious, and conveniently delivered to patients. Bispecific antibodies that target CD3 and CD20 offer an off-the-shelf therapy option with potential advantages to patients with relapsed or refractory B-cell non-Hodgkin lymphoma who are ineligible for or do not have access to CAR-T therapy or other treatments. This first-in-human phase 1 study of epcoritamab, a subcutaneously administered bispecific antibody targeting CD3 and CD20, met its primary objective of establishing the recommended phase 2 dose in patients with relapsed or refractory B-cell non-Hodgkin lymphoma. Importantly, the maximum tolerated dose was not reached and no dose-limiting toxic effects were observed. Leveraging pharmacokinetic and pharmacodynamic modelling and the observed response rates, as well as the safety profile of epcoritamab, the recommended phase 2 dose for the expansion part of this trial and subsequent clinical trials was established at 48 mg across the B-cell non-Hodgkin lymphoma histologies. Epcoritamab was well tolerated and had a manageable safety profile, with no treatment-related adverse events leading to discontinuation or death, no cases of neutropenic fever, and no grade 3 or higher CRS events. All CRS events were resolved with standard-of-care CRS management strategies based on local institutional protocols, without the need for vasopressors or high-flow oxygen. These findings suggest that subcutaneous administration and step-up dosing of epcoritamab in conjunction with corticosteroid prophylaxis were effective in mitigating the risk of high-grade CRS events.

As a single agent, epcoritamab showed antitumour activity in heavily pretreated patients with B-cell non-Hodgkin lymphoma, including those with relapsed or refractory diffuse large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma. Clinically relevant response rates were observed at doses of 48 mg (88% overall response rate, 38% complete response) and 48–60 mg (91% overall response rate, 55% complete response) in patients with relapsed or refractory diffuse large B-cell lymphoma. In addition, responses were seen in all four patients with relapsed or refractory diffuse large B-cell lymphoma who previously received CAR-T therapy. High response rates were also observed in patients with relapsed or refractory follicular lymphoma who received subcutaneous epcoritamab doses of 12–48 mg, with an overall response rate of 80% and a complete response rate of 60% for this dose range. Complete response rates might have been underestimated as PET-CT scans were not initially mandated. Interestingly, responses were observed in two of four patients with relapsed or refractory mantle cell lymphoma (50% overall response rate; 25% had a complete response and 25% a partial response); those patients had the blastoid or pleomorphic variant of mantle cell lymphoma, which is challenging to treat and carries a poor prognosis.[24] Immune response profiles appeared consistent with the observed clinical activity and supported the potential benefit of epcoritamab in this study, as evidenced by robust and sustained B-cell depletion and concomitant activation and expansion of peripheral CD4+ and CD8+ T cells and modest increases in cytokine concentrations.

As in clinical trials of other CD3+ T-cell-engaging agents, including CAR-T therapy,[16,25–30] CRS symptoms

(eg, chills, fever, hypotension, and hypoxia) were also commonly observed with epcoritamab; however, all were manageable and none were severe (no grade 3 or higher CRS events). Furthermore, no correlation between the incidence of CRS and epcoritamab dose was observed. Neurological events ranging from confusion to cerebral oedema have been observed with agents targeting CD3, including blinatumomab (a bispecific antibody targeting CD3 and CD19), as well as with CAR-T therapy.[16,25–30] Of the 68 patients treated with epcoritamab in this study, four had neurological adverse events of special interest that were reported to be consistent with immune-mediated neurological events, and only two of these patients had grade 3 or higher neurological adverse events (grade 3 hypersomnia and grade 3 confusion and depressed level of consciousness).

This is the first published report on the dose-finding study of epcoritamab and results support further clinical development of this novel agent. Caution should be applied when extrapolating these results beyond the study endpoints due to the limitations of the study, including the small sample size and short duration of follow-up. The phase 2 expansion part of this study is ongoing and will serve to validate findings from the dose-escalation study and provide longer follow-up of safety and clinical response outcomes in a larger population of patients with relapsed or refractory B-cell non-Hodgkin lymphoma.

With subcutaneous dosing, epcoritamab might be an attractive alternative to other anti-lymphoma immunotherapies due to its convenience and manageable safety profile. Furthermore, epcoritamab is an investigational agent and a readily available, off-the-shelf option, and its production can be scaled up to meet demand.

In conclusion, the primary endpoint of the trial was met, as the recommended phase 2 dose was established with no dose-limiting toxic effects. Epcoritamab showed potent, single-agent, antitumour activity and an overall manageable safety profile. Coupled with the mechanism of action and ease of administration of epcoritamab, these findings are highly encouraging for patients with relapsed or refractory B-cell non-Hodgkin lymphoma. Epcoritamab is currently being studied in a range of trials including other phase 1/2 studies, as a single agent or in combination with other anti-lymphoma therapies across a range of B-cell non-Hodgkin lymphoma histologies, in the relapsed or refractory setting as well as in previously untreated patients. Furthermore, epcoritamab is being evaluated versus investigator choice of standard-of-care chemotherapy in a phase 3 trial in patients with relapsed or refractory diffuse large B-cell lymphoma (NCT04628494).

Contributors

MH, PJL, TA, BE, RSO, CC, TL, and KC designed the study. AA, CC, TL, KC, and DD did the data collection. All authors contributed to data analysis and interpretation, had full access to and verified all the data in the study, and had final responsibility for the decision to submit for publication. KC served as the study's statistician. All authors were involved in drafting and providing critical revision of the Article.

Declaration of interests

MH reports research support from Genmab, during the conduct of the study; and research support from Takeda, Roche, Celgene, Incyte, Janssen, and Novartis, and personal fees from Takeda and Roche, outside the submitted work. MRC reports personal fees (advisory board) from Janssen and AbbVie, travel reimbursement from AbbVie and Gilead, and consultancy fees from Gilead, outside the submitted work. PJ reports personal fees and non-financial support from Genmab during the conduct of the study. MEDC reports research support from Gilead, Genmab, and Celgene, outside the submitted work. ASB reports travel support from Janssen and has served on advisory boards for Janssen, Celgene, and Amgen, outside the submitted work. DC reports grant support from Amgen, Sanofi, Merrimack, AstraZeneca, Celgene, MedImmune, Bayer, 4SC, Clovis, Eli Lilly, Janssen, and Merck, outside the submitted work. PJL reports grant support from Takeda, Servier, and Roche, personal fees from Genmab, Regeneron, Celgene, Takeda, Servier, Roche, and Incyte, and non-financial support from Celgene, outside the submitted work. RSO, BE, DD, AA, CC, TL, KC, and TA are employees of Genmab and own stock options. All other authors declare no competing interests.

Data sharing

Clinical trial data can be requested by qualified researchers for use in rigorous, independent, scientific research as long as the trials are not part of an ongoing or planned regulatory submission. Sharing of data is subject to protection of patient privacy and respect for the patient's informed consent. The data will be provided following review and approval of a research proposal and statistical analysis plan and execution of a Data Sharing Agreement. For approved requests, the data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, contact clinicaltrials@genmab.com.

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