Subcutaneous Epcoritamab in Patients With Relapsed/Refractory B-cell Non-Hodgkin's Lymphoma: Results From the Dose-Escalation Part of a First-in-Human, Open-Label, Phase 1/2 Study

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SUMMARY

Background: Patients with relapsed or refractory (R/R) B-cell non-Hodgkin's lymphoma (B-NHL) have limited treatment options. Epcoritamab is a novel, CD3xCD20 bispecific antibody that induces T-cell–mediated cytotoxic activity against CD20-positive (CD20+) malignant B cells.

Methods: In this phase 1 first-in-human dose-escalation study (NCT03625037) of subcutaneous (SC) epcoritamab in patients with R/R CD20+ B-NHL, patients received priming and intermediate doses followed by escalating full doses (0·0128-60 mg) of SC epcoritamab administered in 28-day cycles. The primary objectives were to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D). Safety, antitumor activity, and immune biomarkers were also assessed.

Findings: Sixty-eight patients with relapsed, progressive, or refractory CD20+ mature B-NHL received escalating full doses (0·0128-60 mg) of SC epcoritamab. No dose-limiting toxicities were observed, and the MTD was not reached; the full dose of 48 mg was identified as the RP2D. Common adverse events (AEs) were pyrexia (69%), primarily associated with cytokine release syndrome (CRS; 59%; all grade 1-2), and injection site reactions (47%; all but one were grade 1). There were no grade ≥3 CRS events, or discontinuations due to treatment-related AEs or death. Overall response rates (ORR) in R/R diffuse large B-cell lymphoma patients were 68% with 46% achieving complete response (CR) at full doses of 12-60 mg. At 48 mg, the ORR was 88% with 38% CR. Patients with R/R follicular lymphoma had an ORR of 90% with 50% CR at full doses of 0.76-48 mg. Epcoritamab induced robust and sustained B-cell depletion, CD4+/CD8+ T-cell activation and expansion, with modest increases in cytokine levels.

Interpretation: This study met its primary objectives and demonstrated the safety and antitumor activity of single-agent SC epcoritamab in patients with R/R B-NHL, which supports ongoing phase 2 and phase 3 evaluation of epcoritamab.

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RESEARCH IN CONTEXT

Evidence before this study

We searched the PubMed database using the search terms bispecific antibody, CD3, CD20, and relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL) to identify articles that were published in any language from the date of database inception to March 19, 2021. In addition, we conducted a search for these terms in published abstracts from large-scale, globally attended congresses in hematology and oncology, which included congresses sponsored the American Society of Clinical Oncology, the American Association of Clinical 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 therapy and excluded any conference abstracts related to epcoritamab. We identified a total of four published articles and six published congress abstracts describing the most up-to-date results from clinical studies of bispecific antibodies targeting CD3 and CD20 in patients with R/R B-NHL. Two published articles described results in patients who received intravenous (IV) administration of CD20Bi-armed anti-CD-3–activated T cells. One article described a pilot study of three patients with high-risk or R/R diffuse large B-cell lymphoma (DLBCL) who received post-transplant IV CD20Bi-armed activated T cells in combination with low-dose interleukin 2, and the other described a phase 1 study of 12 patients with high-risk or refractory B-NHL (DLBCL, n=11; follicular lymphoma, n=1) who received IV CD20Bi-armed activated T cells after transplantation. Both studies showed that infusion of CD20Bi-armed activated T cells was safe and induced anti-lymphoma cell immunity without inhibiting engraftment; no outcomes related to antitumor activity were reported. Another article described outcomes in 10 pediatric patients with CD20+ B-cell lymphomas, including six with R/R B-NHL (R/R DLBCL, n=3; and R/R Burkitt lymphoma, n=3) who received daily (10, 20, 50, 100, 200, 500, or 1000 μg) or weekly (10, 20, or 50 μg) IV FTBA05. Of the six patients with R/R B-NHL, one with R/R DLBCL achieved a complete response (CR) with FTBA05 alone without donor lymphocyte infusion or chemotherapy. Finally, an article reported results from the phase 1 dose-escalation part of a phase 1/2 study of glofitamab, a CD3xCD20 (2:1 format) bispecific antibody administered intravenously in 174 patients with R/R B-NHL, which included patients with DLBCL (42·7%), transformed follicular

lymphoma (FL) (25·7%), or other aggressive B-NHL (1·8%). Across the dose range, the overall response rate (ORR) was 53·8% with 36·8% of patients achieving CR. At the recommended phase 2 dose (RP2D), the ORR was 65·7% with 57·1% of patients achieving CR. Overall, 50·3% of patients experienced cytokine release syndrome (CRS); 3·5% of patients experienced grade ≥3 CRS. Due to increasing frequency and severity of CRS observed with increasing dose levels, step-up dosing was introduced in the last part of the dose-escalation study. At the highest flat dose, all patients experienced CRS with grade ≥3 CRS occurring in 25% of patients. In the 35 patients treated with step-up dosing at the RP2D, 71·4% experienced CRS, including grade ≥3 CRS in 5·8% of patients. Published congress abstracts described results from studies of four other bispecific CD3xCD20 antibodies in development, namely, odronextamab, mosunetuzumab, and CD20-TCB in patients with R/R B-NHL. In a phase 1 study of IV odronextamab, CRs were observed in patients with R/R DLBCL and R/R FL, including DLBCL patients who had received prior chimeric antigen T-cell therapy. One patient experienced grade 4 CRS and seven discontinued due to treatment-related adverse events (AEs). A phase 2 study of odronextamab was initiated, but this trial was subsequently paused in compliance with the US Food and Drug Administration's request for amendments to the study protocol to reduce the incidence of grade ≥3 CRS. Results from the phase 1/1b study showed that administration of subcutaneous (SC) mosunetuzumab using step-up dosing led to high response rates in patients with R/R indolent or aggressive B-NHL. The maximum tolerated dose was not reached and a dose-limiting toxicity (grade 4 neutropenia) was observed at a dose of 1·6 mg; grade ≥3 CRS events were also observed. In a phase 1b study of IV CD20-TCB, high response rates were observed in patients with aggressive B-NHL and FL. Reported CRS events of any grade appeared to be dose related; grade ≥3 CRS was reported in two patients. While the aforementioned bispecific CD3xCD20 antibodies demonstrate the clinical benefit in patients with R/R B-NHL, safety concerns remain with respect to the risk of severe CRS, and all but one require IV administration.

Added value of this study

Epcoritamab is a highly selective and potent bispecific CD3xCD20 antibody that induces T-cell–mediated cytotoxic activity against CD20+ malignant B cells. This phase 1 part of the first-in-human phase 1/2 study of SC epcoritamab evaluated the safety and antitumor activity of escalating doses of

SC epcoritamab in patients with R/R B-NHL. This study demonstrated that SC epcoritamab had a manageable safety profile, notably with no grade ≥3 CRS events, and induced robust single-agent antitumor activity in heavily pretreated patients with R/R B-NHL, which included patients with R/R DLBCL, FL, and mantle cell lymphoma (MCL).

Implications of all the available evidence

As a single agent, SC epcoritamab was safely administered in patients with R/R B-NHL. Step-up dosing, prophylaxis with corticosteroids, and the SC route of administration were believed to help mitigate the severity of cytokine release syndrome. High response rates were observed in patients with R/R DLBCL and FL, and responses were also observed in patients with MCL. These results support the potential use of epcoritamab in patients with B-NHL. The clinical benefit of epcoritamab will be further validated in ongoing phase 2 and 3 trials. Given the poor prognosis of patients with R/R B-cell NHL, and their limited treatment options, epcoritamab shows promise as a potential alternative to standard chemoimmunotherapy regimens in this population.

INTRODUCTION

Despite recent advances in chemoimmunotherapy (CIT) strategies, management of patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL) is challenging.[1] Treatment of aggressive R/R B-NHL in younger fit patients consists of high-dose chemotherapy and autologous stem cell transplantation (ASCT).[2,3] At least 50% of patients experience a 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 CIT are also seen in patients with R/R indolent B-NHL,[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 R/R B-NHL necessitated 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 given once to eligible patients at certified centers,[12] presents an important advance in the treatment of R/R aggressive B-NHL. 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 may serve as alternative therapy options. To this end, development of bispecific immunologic agents, which target both tumor cells and T cells in patients with hematologic malignancies was initiated. Blinatumomab was the first bispecific immunotherapeutic agent targeting both CD19 on tumor cells and CD3 on T cells to be approved for a hematologic malignancy and is indicated in the treatment of R/R acute lymphoblastic leukemia based on results from a phase 2 trial.[13] As CD20 is a validated therapeutic target in B-cell malignancies, the development of bispecific antibodies (bsAbs) that cross-link CD20 on malignant cells and CD3 on T cells was initiated.[14-16]

Epcoritamab is a full-length IgG1 bispecific antibody consisting of a humanized mouse anti-human CD3 monoclonal antibody and a human anti-CD20 monoclonal antibody.[14] Epcoritamab was created via the controlled FAB arm exchange method using the DuoBody® technology platform, which allows

for retention of native IgG1 structure and a long plasma half-life.[14] Accordingly, DuoBody molecules show normal binding to the neonatal Fc receptor (FcRn), resulting in the 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 FcγR-mediated CD3 crosslinking, while preserving FcRn binding.[14]

In preclinical studies, epcoritamab induced selective, potent T-cell–mediated cytotoxic activity against CD20-positive (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 (mAbs) that induce T-cell cytotoxicity through Fc-mediated effector functions.[14] Compared with three other CD3xCD20 bsAb analog constructs, 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 to 3·5 pM.[14] Notably, this finding translated into epcoritamab retaining its anti-tumor activity *in vivo* in the presence of a rituximab analog. Subcutaneous (SC) administration of epcoritamab is supported by an in vivo study in cynomolgus monkeys, which demonstrated a similar degree of prolonged B-cell depletion with SC and intravenous (IV) administration. Importantly, SC administration also resulted in delayed and lower peak cytokine levels,[14] suggesting that the SC route of administration could potentially reduce the risk of severe cytokine release syndrome (CRS). Epcoritamab also demonstrated cytotoxic activity in malignant B cells isolated from patients with B-NHL who were previously treated with CD20 antibodies as well as in newly diagnosed patients.[17]

Overall, these findings led to the initiation of a first-in-human (FIH) phase 1/2 dose-escalation and expansion trial of SC epcoritamab in patients with R/R B-NHL (NCT03625037). We report findings from the phase 1 dose-escalation part of this ongoing study, where the primary objectives were to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D).

METHODS

Study design and patient population

This FIH, multicenter, open-label, phase 1/2 trial (NCT03625037) was initiated in June 2018 and consisted of a dose-escalation part and an ongoing dose-expansion part. Patients enrolled from 10 sites across four countries (Denmark, Netherlands, United Kingdom, and Spain) (**Appendix Table S1**) were assigned to SC epcoritamab injections with predefined step-up and target doses. Dose escalation was conducted using a modified Bayesian Optimal Interval (mBOIN) design, which provided greater flexibility than the standard 3+3 design (**Appendix Figure S1**).[18] In this trial, the target dose-limiting toxicity (DLT) rate was set at 30% with boundaries λe=0·236 and λd=0·359. Modification of BOIN escalation and de-escalation rules includes exemptions in the case of 6 or 9 DLT-evaluable patients, and utilization of both accelerated and standard titration parts.

The decision to escalate to the next highest dose was determined by comparing the observed rate of dose-limiting toxicities (DLTs) with the two predetermined fixed boundaries (0·236 and 0·359) and with the target DLT rate of 30%, falling between the two boundaries. Details related to dose escalation stopping criteria are outlined in the **Appendix**. The DLT evaluation period spanned the first 4 weeks (i.e., 28 days) after the first administration of SC epcoritamab. No dose modifications were allowed during the study, but dose interruptions were permitted. A patient who experienced a DLT could continue epcoritamab therapy if DLT severity decreased to grade ≤2 or baseline within 4 weeks. The Data Monitoring Committee reviewed all available data and evaluated newly emergent safety data including DLTs and provided the Sponsor Safety Committee with recommendations for the next dose level.

The study population for the dose escalation part consisted of adults (aged ≥18 years) with relapsed, progressive, or refractory CD20+ mature B-NHL (including patients with diffuse large B-cell lymphoma [DLBCL; de novo or transformed], high-grade B-cell lymphoma [HGBCL], primary mediastinal large B-cell lymphoma [PMBCL], follicular lymphoma [FL], mantle cell lymphoma [MCL], small lymphocytic lymphoma [SLL], and marginal zone lymphoma [MZL]).[19] Demonstration

of CD20 positivity based on local pathologic evaluation was required; however, the method or threshold to verify CD20 positivity was not specified. Eligible patients were required to have previous treatment with an anti-CD20 mAb-containing regimen and be ineligible to all standard therapeutic options. Patients were required to have measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and adequate renal and hepatic function. Patients were excluded if they had central nervous system (CNS) lymphoma (or known CNS involvement), received CAR-T cell therapy within 30 days prior to the first dose of epcoritamab, had chronic or ongoing infections, or required immunosuppressive therapy. Patients who received prior allogeneic stem cell transplantation (SCT) or solid organ transplantation were excluded (complete inclusion/exclusion criteria are outlined in **Appendix Table S2)**.

Treatment administration

In the phase 1 dose-escalation part of the study, patients received SC epcoritamab using a step-up approach, which entailed administration of predefined priming/intermediate doses over a 2-week period, followed by full doses ranging from 0·0128 mg to 60 mg by cohort (**Appendix Figure S2**). The step-up dosing approach was intended to mitigate the severity of CRS. Patients received the priming dose of SC epcoritamab on Day 1 of Cycle 1 and the intermediate dose on Day 8 of Cycle 1. Full-dose SC epcoritamab (1mL) 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 IV or equivalent), antipyretics (paracetamol [acetaminophen] 650-1000 mg oral or equivalent), and antihistamines (diphenhydramine 50 mg IV or oral or equivalent) was administered 30 to 120 minutes before the first four SC epcoritamab injections (during Cycle 1 and as needed during Cycle 2) as additional measures to mitigate CRS severity. As a further precaution, patients were hospitalized for at least 72 hours after the first and second administrations of epcoritamab and for 24 hours 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 (**Appendix Table S3**).

Patients could receive concomitant medications/treatments for the purpose of receiving adequate care as clinically indicated, and included supportive care for the management of CRS (saline infusion, systemic glucocorticosteroids/antihistamines/antipyretic medications, vasopressin/vasopressors, low-flow/high-flow oxygen or positive-pressure ventilation support, IV tocilizumab), supportive therapy for tumor 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 were also permitted.

Outcomes

The primary endpoints of the dose-escalation part of this FIH trial were determination of the MTD and the RP2D of epcoritamab. Treatment-emergent adverse events (AEs) were evaluated and graded according to Common Terminology Criteria for Adverse Events (v5·0). CRS was graded according to American Society for Transplantation and Cellular Therapy consensus criteria.[20] Clinical tumor lysis syndrome was graded according to Cairo–Bishop criteria.[21] Additional endpoints were anti-tumor activity/treatment response, progression-free survival (PFS), and pharmacokinetic (PK) parameters; pharmacodynamic (PD)/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) positron emission tomography (PET) computed tomography (CT) scans or FDG-PET with CT or magnetic resonance imaging (MRI) when combined PET-CT scans were not available. Initially, PET scans were not required for disease evaluation but were later implemented after a protocol amendment (November 4, 2019). Treatment responses during dose escalation were evaluated based on 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 prior to the start of subsequent anti-lymphoma therapy. For patients who remained alive without a post-baseline tumor assessment, PFS was censored on the first dosing date. PK analyses of epcoritamab were performed in blood samples obtained at prespecified time points (**Appendix Table S4**).

An integrated semi-mechanistic PK/PD modelling approach, which incorporated preclinical PK/PD data from cynomolgus monkeys as well as clinical PK, biomarker, exposure–response, and exposure–safety analyses from this study, were used to determine the RP2D. The PK/PD model was calibrated using clinical exposure–response data (**Appendix**). The calibrated PK/PD model was used to simulate DLBCL and FL based on differences in tumor growth rates to predict trimer formation.

An exploratory analysis of potential biomarkers associated with clinical response to epcoritamab was conducted using peripheral blood samples obtained at screening and during treatment to evaluate the effects of treatment on circulating immune cells (**Appendix Table S4**). Whole-blood flow cytometry and enzyme-linked immunosorbent assays were used to detect immune cells and plasma cytokine levels, respectively.

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 Figure S1**). No formal sample size calculations or statistical hypotheses were implemented in the dose-escalation part of this study. Categorical data were summarized and presented as frequencies and percentages. Continuous data were summarized by the number of non-missing values with determination of mean (standard deviation) and median (interquartile range [IQR]). No imputation of missing data was performed for safety and PK endpoints. Time-to-event parameters were described using Kaplan–Meier estimates (median time and IQR with approximate 95% confidence intervals [CIs]). Median PFS 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 performed on the safety analysis set, which was the same as the full analysis set 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 and completed the DLT evaluation period with sufficient safety evaluations or experienced a DLT during the DLT evaluation period. The dose-determining analysis population was used in the analysis of the MTD. Data were analyzed using SAS (v9·4) software.

Study oversight and data handling

The study was conducted 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**). All patients reviewed and signed informed consent forms before enrolling in the study. The trial was monitored by the study sponsor. Data were captured using electronic data capture. Trial-site personnel transcribed the data from source documents onto electronic case report forms (eCRFs), which were securely transferred to the study sponsor. All source documents, eCRFs, and other required documents were maintained in compliance with International Council for Harmonisation Good Clinical Practice guidelines. All authors had access to the study data.

Role of the funding source

This study was funded by Genmab A/S and AbbVie Inc., and is registered at ClinicalTrials.gov (NCT03625037). Epcoritamab is being jointly developed by Genmab A/S and AbbVie Inc. The sponsor was involved with data collection, analysis, interpretation, writing of the manuscript, and the decision to submit.

RESULTS

The first patient was enrolled on July 17, 2018. A total of 73 patients were enrolled in the dose-escalation part and 68 received epcoritamab at full doses of ≤24 mg (n=53), 48 mg (n=12), or 60 mg (n=3) (**Figure 1**). Baseline disease characteristics, including prior systemic therapy are shown in **Table 1.** Of the 68 patients enrolled, 46 (68%) had DLBCL, 12 (18%) had FL, four (6%) had MCL, and three (4%) had HGBCL; the remaining three patients had PMBCL, SLL, and MZL based on World Health Organization classification criteria.[19] The majority of patients (94%) had an ECOG performance status of 0-1, all were refractory to or had relapsed after treatment with anti-CD20 mAbs, and almost all (>90%) had received prior chemotherapy. The patients had received a median of three prior lines of therapy and most (87%; n=59/68) were refractory to prior treatment. Six patients had received prior CAR-T therapy. Patients with DLBCL (n=46) had received a median of three prior lines of systemic therapy; seven patients had received prior ASCT and five had received prior CAR-T therapy. Patients with FL (n=12) had received a median of five lines of prior systemic therapy.

As of the data cutoff date of January 31, 2021, 15 of 68 patients (22%) remained on treatment with epcoritamab. The most common reason for discontinuation of study treatment was progressive disease (66%; n=45/68). One patient discontinued treatment due to an unrelated fatal AE (COVID-19 pneumonia). No patients discontinued due to treatment-related AEs.

Epcoritamab exhibited 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 PK/PD model, response rates started to plateau at the 48 mg epcoritamab dose for both FL and DLBCL, which was in line with predicted epcoritamab/CD3/CD20 trimer formation (**Figure 2**). Clinical trial simulation using the calibrated PK/PD model showed that the predicted trial response rate reached a plateau starting at a dose of 48 mg. Increasing the dose beyond 48 mg did not provide any significant increase in the predicted trial response rate. Simulation performed using the fitted PK model to assess PK dose proportionality also showed that saturation of

non-linearity in PK occurs at epcoritamab doses ≥48 mg (**Appendix Figure S3**). Based on one clinical trial simulation using the PK/PD model, exposure–response/exposure–safety analyses, and safety data, 48 mg was identified as the RP2D as well as the lowest biologically effective dose, which resulted in optimal trimer formation and improved clinically relevant responses, while potentially minimizing safety risks.

Median duration of exposure to epcoritamab in the ≤24 mg, 48 mg, and 60 mg dose groups were 8·1 weeks (IQR, 4·1-24·1), 11·8 weeks (IQR, 5·8-30·6), and 40·1 weeks (IQR, 11·0-40·3), respectively. No DLTs or dose reductions occurred during the DLT evaluation period and the MTD was not reached up to the highest dose of 60 mg. The most common treatment-emergent AEs were pyrexia (69%; n=47/68) primarily associated with CRS (59%; n=40/68), and injection site reactions (47%; n=32/68; tenderness, warmth, erythema, itching, and pain) (**Table 2**). Most incidences of pyrexia (91%; n=43/47) were of grade 1/2 severity and all but one incident of injection site reaction (97%; n=31/32) were of grade 1 severity . Serious AEs were reported in 46 patients (68%), the most common being pyrexia, and pneumonia; pyrexia was the only serious treatment-related AE occurring in ≥5% of patients (31%; n=21/68). There were no cases of febrile neutropenia.

AEs of special interest, specifically CRS, neurologic events, and clinical tumor 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 hospitalization. Most CRS events occurred during Cycle 1. The median (IQR) time to onset of the first CRS event after the first priming dose and first full dose was 1·4 days (IQR, 0·9-3·1) and 1·8 days (IQR, 0·8-3·1), respectively. 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 days (IQR, 0·5-3·1) after the first priming dose and 2·2 days (IQR, 0·9-4·6) after the first full dose. All patients who experienced 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 (59%), hypotension (24%), hypoxia (18%), tachycardia

(15%), and chills (10%). Neurologic symptoms possibly related to epcoritamab were reported in four patients who received ≤24 mg doses (grade 1 partial seizure, grade 1 agraphia, grade 3 hypersomnia, and grade 3 confusion and depressed level of consciousness); all were transient (IQR, 2·5-6·0 days) and patients recovered without sequelae. Grade 3 clinical tumor lysis syndrome was observed in a patient with PMBCL in the setting of retroperitoneal hemorrhage related to progression of bulky disease.

Eleven out of 68 died on treatment (all due to disease progression). Overall, including survival follow-up, 38 of the 68 (56%) patients died and disease progression was the most common cause of death (49%; n=33/68). Other causes of death, all post treatment, were COVID-19, 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 AEs.

Antitumor responses were observed in patients with R/R DLBCL (0·76-<12 mg, overall response rate [ORR]=13%; complete response [CR]=13%; 12-60 mg, ORR=68%; CR=46%; 48 mg, ORR=88%; CR=38%; 48-60 mg, ORR=91%; CR=55%) (**Table 4; Figure 3A**). Response data for patients with R/R DLBCL are presented at the RP2D (48 mg) and doses ≥12 mg, which correlated with >90% saturation of nonlinear PK, indicative of saturation of target engagement. In R/R DLBCL patients who received ≥12-mg epcoritamab, the median (IQR) time to response was 1·4 (1·3-2·6) months; median (IQR) time to reach CR was 2·7 (1·3-2·8) months. Treatment response deepened over time, with five patients initially achieving a partial response (PR) at Week 6 that subsequently converted to a CR; the time to conversion ranged from 5·4 weeks to 11·1 weeks. The median (IQR) duration of follow-up for patients who achieved CR was 8·7 months (7·2-13·7). The estimated probability of DLBCL responders maintaining remission for ≥6 months was 75% (95% CI: 46, 90). Six of the 10 patients receiving ≥48 mg SC epcoritamab have ongoing response, with five of these patients achieving CR (**Figure 3B**). At the time of data cutoff, all patients with R/R DLBCL who achieved CR after receiving epcoritamab doses ≥12 mg (median follow-up, 6·5 months; IQR: 5·6-7·4) remained in remission (longest duration of ongoing CR, 11·2+ months). Three patients who achieved CR went on

to receive SCT (ASCT, n=2; allogeneic SCT, n=1) with curative intent; all three patients were in remission at the time of the data cutoff (**Figure 3B**). The median duration of follow-up for R/R DLBCL patients who received prior CAR-T therapy was 5·8 months (IQR: 1·0-7·0). All four evaluable DLBCL patients who had previously received CAR-T therapy (relapsed DLBCL, n=1; refractory DLBCL, n=3) responded to treatment (CR=50% [n=2]; PR=50% [n=2]) (**Figure 3B**); two of these patients proceeded to SCT. Among patients with R/R DLBCL who received <12-mg doses of epcoritamab, ORR was 13% (CR, n=3). Median (IQR) PFS for patients with R/R DLBCL who received epcoritamab doses ≥12 mg was 9.1 months (1.6, not reached). In patients who received doses ≥48 mg median PFS has not been reached (**Figure 3C**).

For assessment of antitumor activity in patients with R/R FL (n=10), a dose threshold of ≥0·76 mg was chosen based on the minimal efficacy threshold and PK/PD modeling. High response rates were observed in patients with R/R FL (0·76-48 mg, ORR=90%; CR=50%) (**Table 4**). The median (IQR) time to response was 1·9 (1·5-3·5) months. Notably, PET scans were not performed in four patients with R/R FL as these were not initially mandatory per protocol; in the absence of PET, CT scans may have failed to detect complete metabolic response. In patients treated with full doses of 12- to 48-mg epcoritamab, the ORR and CR rates were 80% and 60%, respectively. Responses deepened over time in three patients with R/R FL in whom an initial response of PR converted to CR over a period of 6 weeks to 45 weeks; five patients experienced ongoing response at the time of data cutoff (PFS not mature) (**Figure 3D**).

Responses were observed in two of the four evaluable patients with R/R MCL (0·76-48 mg, ORR=50%; CR=25%; PR=25%; **Table 4**, **Figure 3D**) and both patients had the blastoid/pleomorphic variant of MCL. At the time of data cutoff, median (IQR) time to response was 1·4 (1·3-1·5) months. Of the three patients with HGBCL, one who received full doses of 6 mg achieved PR; the remaining two patients each had stable disease and progressive disease after receiving full doses of 6 mg and 0.12 mg, respectively.

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** and **4B**). A transient decrease in circulating peripheral CD4+ and CD56−/CD8+ T cells was observed within 6 hours of the first SC dose of epcoritamab; subsequent dosing elicited expansion of CD4+ and CD8+ T cells after 6 to 8 weeks of treatment (**Appendix Figure S4A** and **S4B**). Step-up dosing with SC epcoritamab was associated with moderate increases in interferon gamma, interleukin 6, and tumor necrosis factor alpha (**Figure 4C**).

DISCUSSION

Despite recent advances in the treatment of R/R B-NHL, there is an unmet need for novel therapeutics that are safe, efficacious, and conveniently delivered to patients. Bispecific CD3xCD20 antibodies offer an off-the-shelf therapy option with potential advantages to patients with R/R B-NHL who are ineligible or do not have access to CAR-T or other treatments. This FIH phase 1 study of epcoritamab, a subcutaneously administered CD3xCD20 bsAb, met its primary objective of determining the RP2D in patients with R/R B-NHL. Importantly, the MTD was not reached and no DLTs were observed. Leveraging PK/PD modeling and the observed response, and safety profile of epcoritamab, the RP2D for the expansion part of this trial and subsequent clinical trials was established at 48 mg across the B-NHL histologies. Epcoritamab was well tolerated and had a manageable safety profile, with no treatment-related AEs leading to discontinuation or death, no cases of neutropenic fever, and no grade ≥3 CRS events. All CRS events 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 SC 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 demonstrated robust antitumor activity in a heavily pretreated B-NHL patients with R/R DLBCL, FL, and MCL. High clinically relevant response rates were observed at doses of 48 mg (ORR=88%; CR=38%) and 48-60 mg (ORR=91%; CR=55%) in patients with R/R DLBCL; all R/R DLBCL patients who achieved a CR with ≥12 mg epcoritamab were in ongoing

remission at the time of data cutoff. In addition, responses were also seen in all four R/R DLBCL patients who previously received CAR-T therapy. High response rates were also observed in patients with R/R FL who received ≥12 mg SC epcoritamab, with an ORR of 80% and a CR rate of 60%. CR rates may have been underestimated as PET-CT scans were not initially mandated (only six of 10 patients with R/R FL underwent response evaluation by PET-CT scans). Interestingly, responses were also observed in two of four patients with R/R MCL (ORR=50%; CR=25% [24 mg]; PR=25% [48 mg]); both patients had the blastoid/pleomorphic variant of MCL, 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 levels.

As in clinical trials of other CD3 T-cell–engaging agents including CAR-T-therapy,[13,16,25-29] CRS symptoms (chills, fever, hypotension, and hypoxia) were also commonly observed with epcoritamab; however, all were manageable and none were severe (no grade ≥3 CRS events). Furthermore, no correlation between the incidence of CRS and epcoritamab dose was observed. Neurologic events ranging from confusion to cerebral edema have been observed with agents targeting CD3, including other CD3xCD20 bsAbs and bispecific T-cell engagers, as well as with CAR-T therapy.[13,16,25-29] Of the 68 patients treated with epcoritamab in this study, four had neurologic AEs of special interest that were reported to be consistent with immune-mediated neurologic events, and only two of these patients had grade ≥3 neurologic AEs (grade 3 hypersomnia, grade 3 confusion, and depressed level of consciousness).

This is the first published report on the dose-finding study of epcoritamab and the results support further clinical development of this novel agent. Caution should be applied when extrapolating these results beyond the study endpoints due to 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 R/R B-NHL population.

With SC dosing, epcoritamab may 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 determined with no dose-limiting toxicities. Epcoritamab demonstrated potent, single-agent antitumor activity and overall manageable safety profile of epcoritamab. Coupled with its mechanism of action and ease of administration, these findings are highly encouraging for R/R B-NHL patients. 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-NHL histologies, in the R/R 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 R/R DLBCL (NCT04628494).

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AUTHOR CONTRIBUTIONS

MH, PJL, TA, BE, RO, CC, TL, and KC designed the study. AA, CC, TL, KC, and DD performed data collection. All authors performed data analysis and interpretation, had full access 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.

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M Hutchings reports research support from Genmab during the conduct of the study. Outside the submitted work, he also reports research support and personal fees from Takeda, and Roche and reports research support from Celgene, Incyte, and Novartis.

R Mous declares no competing interest.

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D Lewis declares no competing interest.

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DATA SHARING STATEMENT

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 Data. 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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FIGURE LEGENDS

Figure 1. Patient Disposition. *The safety analysis set was defined as all patients who received at least one dose of epcoritamab.

Figure 2. Simulated Exposure of Epcoritamab. Clinical trial simulation was performed using the calibrated PK/PD model. At each dose level, 100 trials were simulated. The box plot summarizes response rate from 100 simulated trials. In each trial, simulations were performed for 128 patients and the overall response rate of each simulated trial was calculated based on change in tumor size for each simulated patient. Simulations for DLBCL and FL were differentiated based on differences in tumor doubling times (DLBCL, ~1 month; FL, ~6 months) reported in the literature. Abbreviations: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.

Figure 3. Treatment Response in Patients With DLBCL, FL, and MCL

A. Best Percent Change From Baseline in Tumor Size (Modified Response Evaluable Set; N=66). B. Response Profile in Patients With DLBCL. C. Response Profiles in Patients With FL or MCL. 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 due to coronary artery bypass surgery. A PET scan was not initially required for FL; protocol amendment added PET follow-up of all FDG-avid disease. †Excludes one patient with FL who died before post-baseline assessment. ‡Excludes one patient with MCL who died before post-baseline assessment. §Excludes two patients with DLBCL; 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 enrollment. Abbreviations: CAR-T, chimeric antigen receptor T-cell therapy; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FDG, fluorodeoxyglucose; FL, follicular lymphoma; MCL, mantle cell lymphoma; HSCT, hematopoietic stem cell transplantation; PD, progressive disease; PET, positron emission tomography; PR, partial response.

Figure 4. Changes in Immune Cell Populations and Cytokine Levels in Patients Treated With Epcoritamab. A. Change in Peripheral B-Cell Levels Over Time After Treatment With SC Epcoritamab (colored lines represent individual patients). B. T-Cell Expansion in Peripheral Blood After Administration of SC Epcoritamab: All Patients ≥12 mg Epcoritamab. C. Longitudinal Change in Median Cytokine Levels After Administration of SC Epcoritamab: Interferon Gamma: All Patients ≥12 mg Epcoritamab (upper), Interleukin 6: All Patients ≥12 mg Epcoritamab (middle), and Tumor Necrosis Factor Alpha: DLBCL ≥12 mg Epcoritamab (lower). Median values are shown; error bars represent the interquartile range. Vertical dashed lines represent administration of epcoritamab. Horizontal dashed lines represent the lower limit of reporting. Abbreviations: DLBCL, diffuse large B-cell lymphoma; IFN-γ, interferon gamma; IL-6, interleukin 6; LLOR, lower limit of reporting; log, logarithm; SC, subcutaneous; TCR, T-cell receptor; TNF-α, tumor necrosis factor alpha.

TABLES AND FIGURES

Table 1. Demographics and Baseline Characteristics

Characteristic	R/R DLBCL (N=46)	R/R FL (N=12)	All Patients (N=68)*
Age, years, median (IQR)	68 (55-74)	73 (63-76)	68 (56·5-75)
Male, n (%)	30 (65)	8 (67)	45 (66)
ECOG performance status, n (%)			
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, n (%)			
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)
Extra-nodal disease, n (%)	29 (63)	6 (50)	42 (62)
Median time since diagnosis, months (IQR)	25·4 (11·0-54·6)	61·5 (34·3-153·1)	29·7 (13·7-66·8)
Median time since relapse or progression, months (IQR)	1·5 (1·1-2·3)	1·6 (1·2-2·6)	1·6 (1·1-2·3)
Median number of lines of prior therapy (IQR)	3 (2·0-4·0)	5 (2·5-8·0)	3 (2·0-4·5)
Prior therapies, n (%)			
Anti-CD20 mAb	46 (100)	12 (100)	68 (100)
Anthracyclines	46 (100)	9 (75)	62 (91)
Alkylating agents	46 (100)	12 (100)	67 (99)
Autologous SCT	5 (11)	1 (8)	7 (10)
CAR-T	5 (11)	0	6 (9)
Treatment-refractory patients by therapy, n (%)			
Last line of systemic therapy	42 (91)	10 (83)	59 (87)
Alkylating agents	40 (87)	9 (75)	56 (82)
CD20 mAbs	42 (91)	10 (83)	60 (88)

*Ten patients had other B-NHL histologies including MCL (n=4), HGBCL (n=3), PMBCL (n=1), SLL (n=1), and MZL (n=1).

†During the screening period, one patient with follicular lymphoma had an ECOG performance status of 2 and met the inclusion criteria; however, prior to dosing on Day 1 of Cycle 1, the patient was found to have an ECOG performance status of 3; based on the full analysis principle, this patient was included in the study.

Abbreviations: B-NHL, B-cell non-Hodgkin lymphoma; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; IQR, interquartile range; mAb, monoclonal antibody; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PMBCL, primary mediastinal B-cell lymphoma; SCT, stem cell transplantation; SLL, small lymphocytic leukemia.

Table 2. Treatment Emergent Adverse Events ≥20% (Full Analysis Population; N=68)

AEs by Preferred Term, n (%)	AE Severity		
	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	25 (38)	4 (6)	0
Diarrhea	18 (26)	0	0
Hypotension*	17 (25)	4 (6)	0
Dyspnea	16 (24)	0	1 (1)
Tachycardia*	14 (21)	0	0
Anemia	7 (10)	9 (13)	0

*Most pyrexia, hypotension, and tachycardia events were associated with cytokine release syndrome.
Abbreviations; AE, adverse event.

Table 3. Adverse Events of Special Interest (Full Analysis Population; N=68)

AE, n (%)	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)
Neurologic 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 tumor lysis syndrome				
Total	0	1 (8)	0	1 (1)
Grade 3	0	1 (8)	0	1 (1)

Abbreviation: AE, adverse event.

Table 4. Treatment Response by Diagnosis (Modified Response Evaluable Set; N=66)*

Response parameter[¥], n (%)	R/R DLBCL[†]			R/R FL**		R/R MCL[‡]	
	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)
ORR, n (%) (95% CI)	15 (68) (0·451, 0·861)	7 (88) (0·473, 0·997)	3 (100) (0·292, 1·000)	9 (90) (0·555, 0·997)	0 (0·00, 0·975)	2 (50) (0·068, 0·932)	1 (100) (0·025, 1·000)
CR, n (%)	10 (46)	3 (38)	3 (100)	5 (50)	0	1 (25)	0
PR, n (%)	5 (23)	4 (50)	0	4 (40)	0	1 (25)	1 (100)
SD, n (%)	1 (5)	0	0	0	0	1 (25)	0
PD, n (%)	5 (23)	0	0	1 (10)	1 (100)	0	0
Median time to response, months (IQR)	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)
Median follow up duration, months (IQR)	7·4 (2·7-9·6)	7·4 (4·4-8·3)	9·2 (5·5-9·3)	11·9 (9·9-16·4)	6·6 (6·6-6·6)	8·9 (4·0-10·3)	7·7 (7·7-7·7)

*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 R/R DLBCL who discontinued before first assessment due to COVID-19 pneumonia and one patient with R/R FL who discontinued before first assessment due to coronary artery bypass (CABG) surgery. Data are not shown for 23 patients with R/R DLBCL who received <12 mg doses and for six additional patients with other R/R B-NHL histologies.

[€]Includes one patient who died before response assessment.

[¥]Response assessments were based on Lugano classification response criteria (Cheson BD, et al. *J Clin Oncol*. 2014) by investigator assessment.

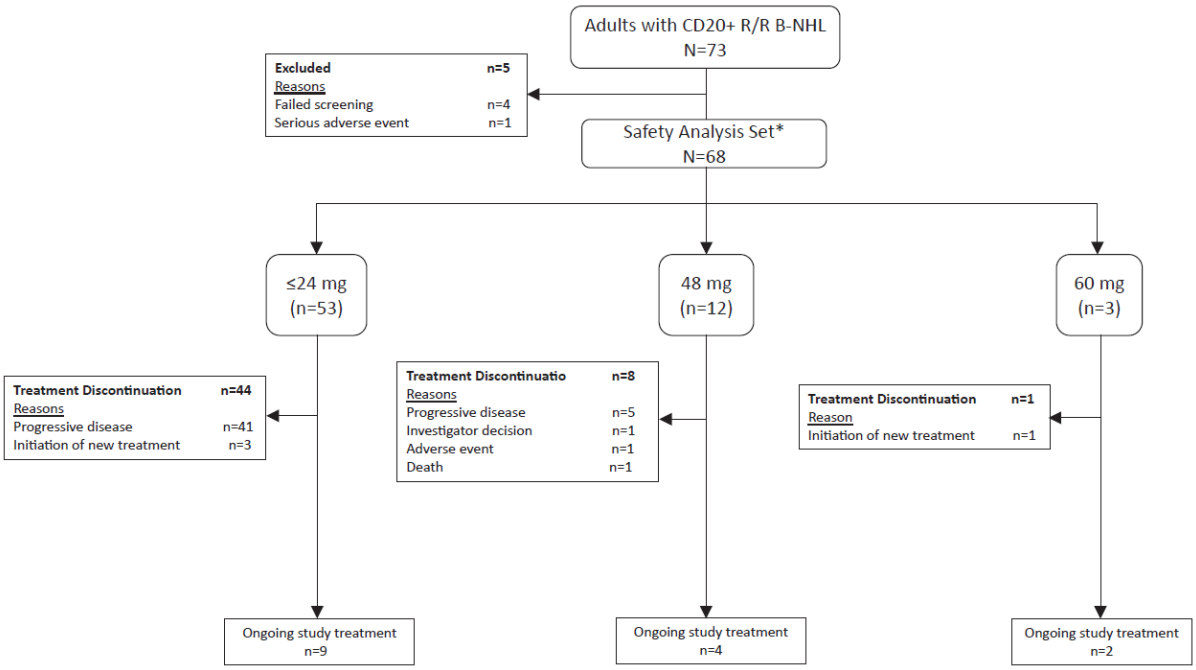
†Includes 3 patients who received the 60-mg dose before RP2D was determined.

[‡]One patient had blastoid/pleomorphic MCL; one had unknown histology.

**Six of the 10 patients had response evaluation by PET scans (not mandatory until a protocol amendment on November 4, 2019).

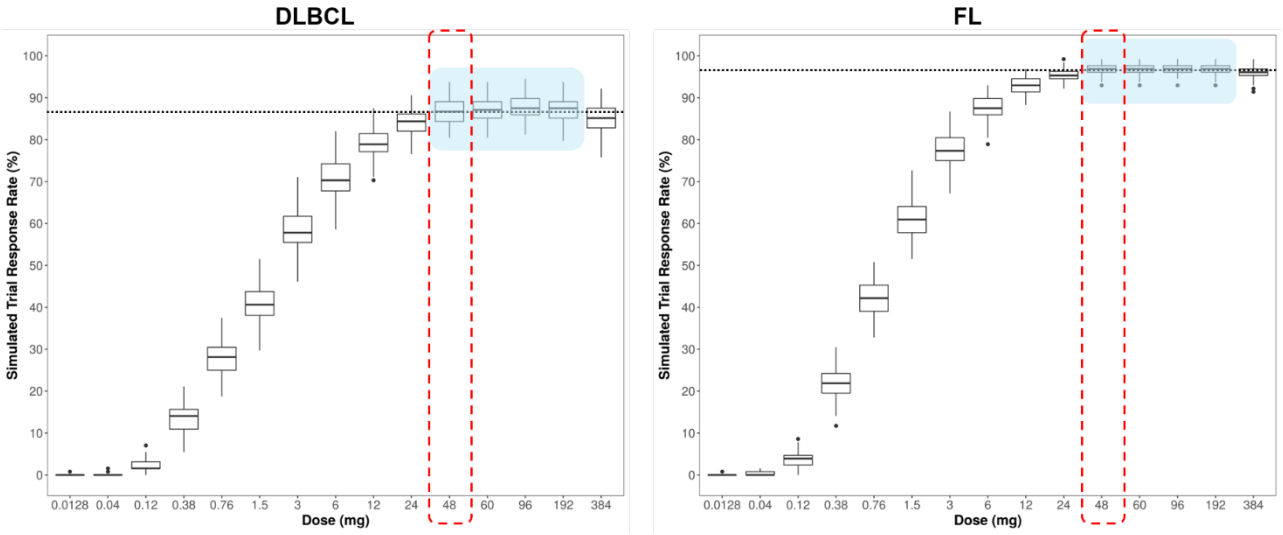
Abbreviations: CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IQR, interquartile range; MCL, mantle cell lymphoma; NA, not applicable; PD, progressive disease; PR, partial response; RP2D, recommended phase 2 dose; R/R, relapsed or refractory; SD, stable disease.

Figure 1. Patient Disposition



*The safety analysis set was defined as all patients who received at least one dose of epcoritamab.

Figure 2. Simulated Exposure of Epcoritamab



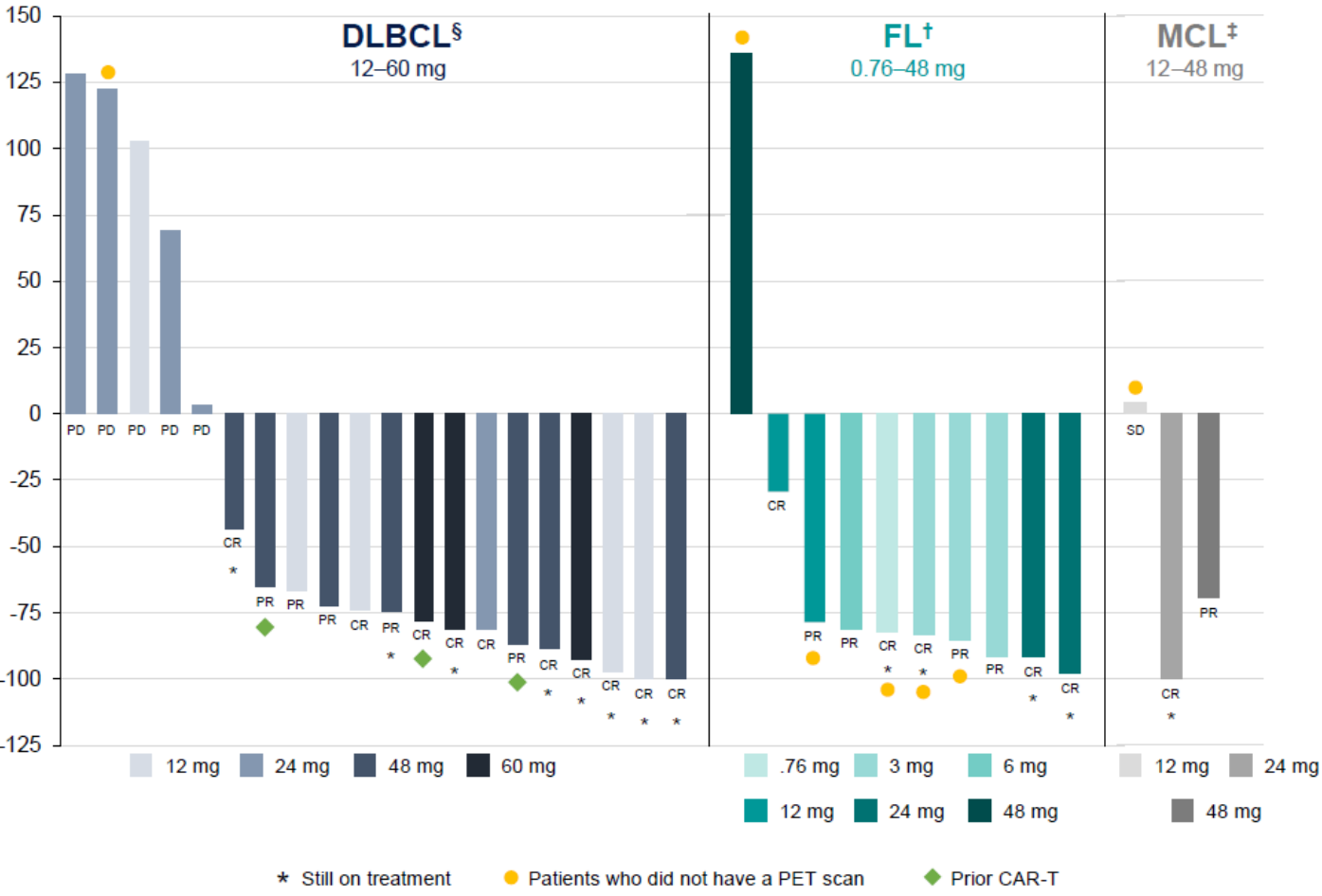
Abbreviations: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.

Data cutoff October 19, 2020

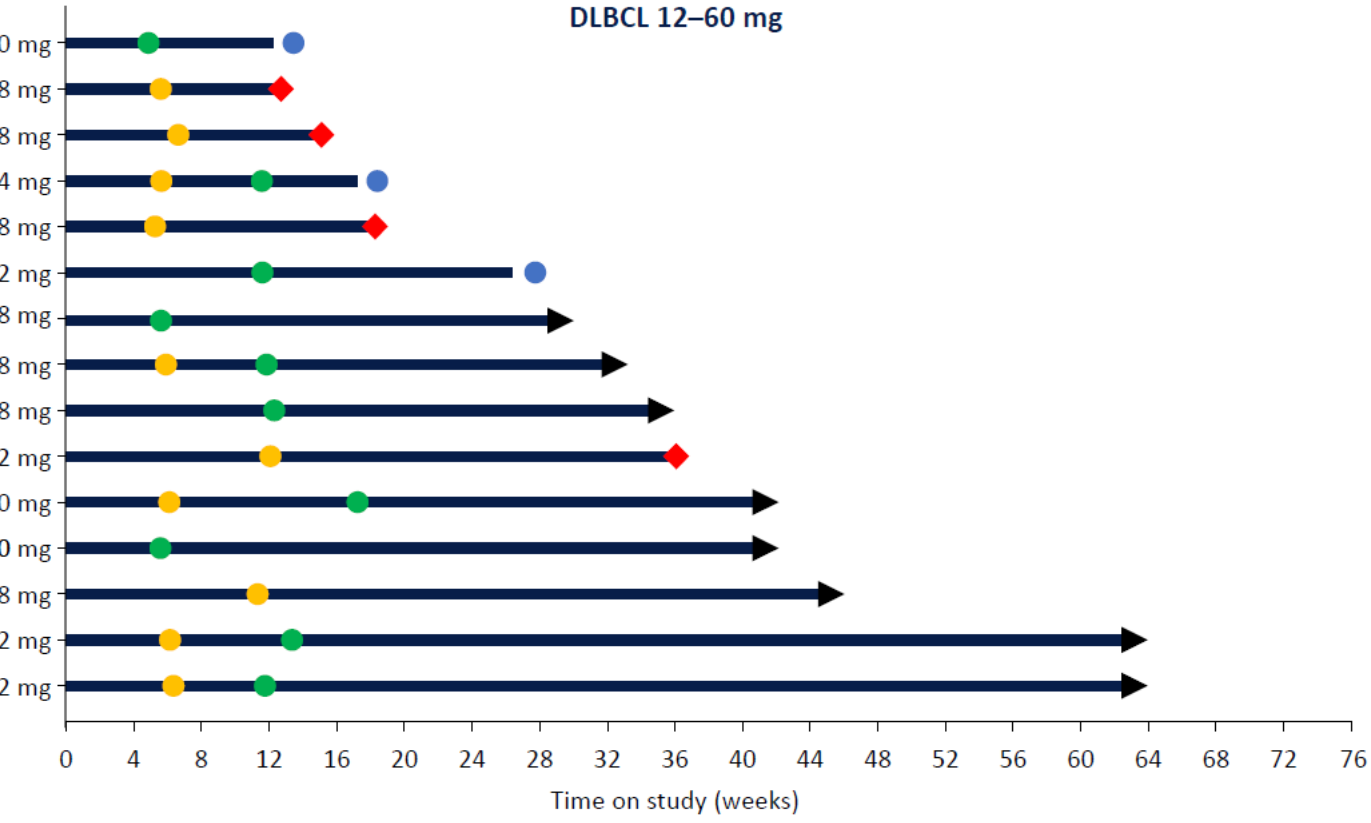
Clinical trial simulation was performed using the calibrated PK/PD model. At each dose level, 100 trials were simulated. The box plot summarizes response rate from 100 simulated trials. In each trial, simulations were performed for 128 patients and the overall response rate of each simulated trial was calculated based on change in tumor size for each simulated patient. Simulations for DLBCL and FL were differentiated based on differences in tumor doubling times (DLBCL, ~1 month; FL, ~6 months) reported in the literature.

e 3. Treatment Response in Patients With R/R DLBCL, FL, and MCL

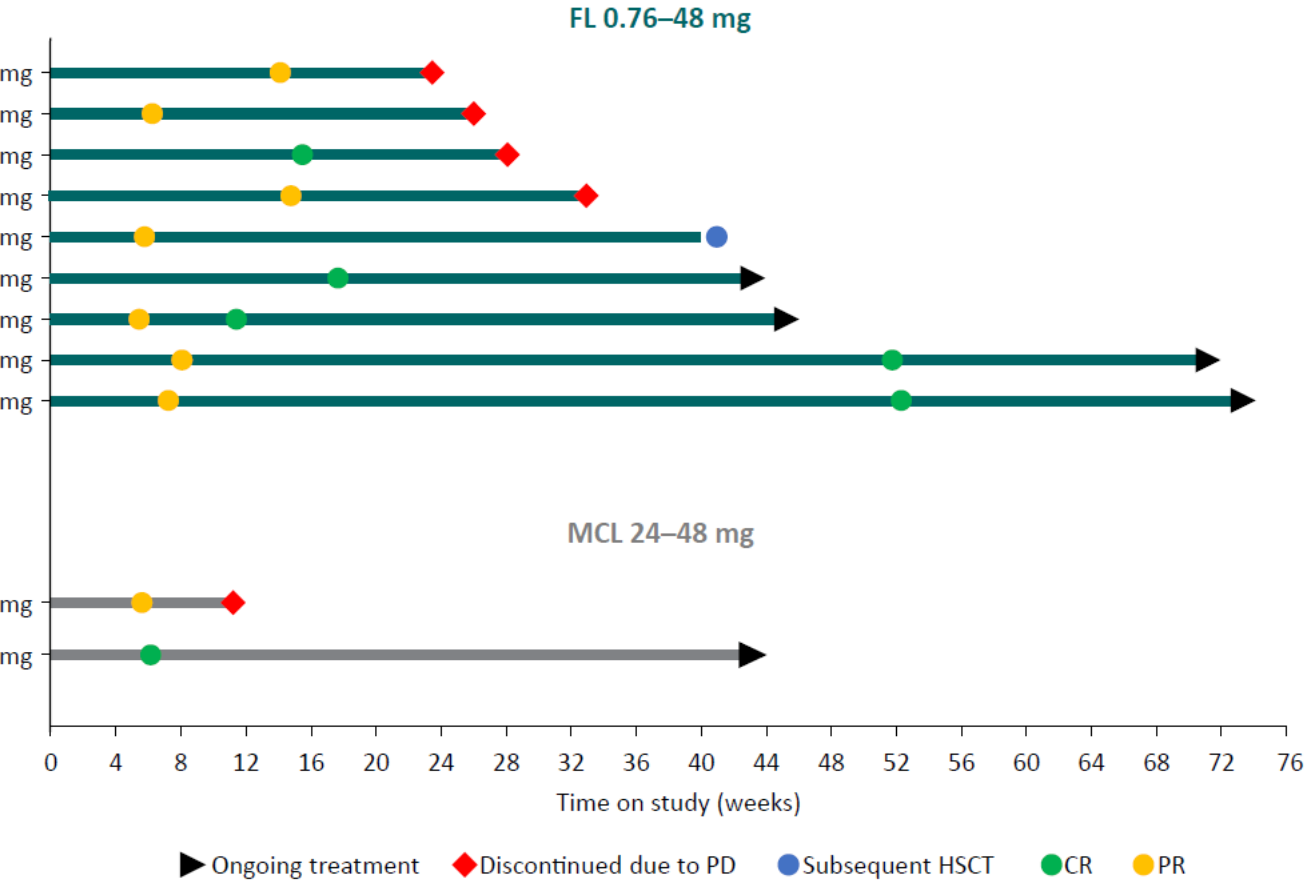
st Percent Change from Baseline in Tumor Size (Modified Response Evaluable Set; N=66)



sponse Profile in Patients With R/R DLBCL



sponse Profiles in Patients With R/R FL or MCL



re shown for the modified response-evaluable population, which excluded one patient with COVID-19 pneumonia and one patient who discontinued first assessment due to coronary artery bypass surgery. A PET scan was not initially required for FL; protocol amendment added PET follow-up of a avid disease.

des one patient with FL who died before post-baseline assessment.

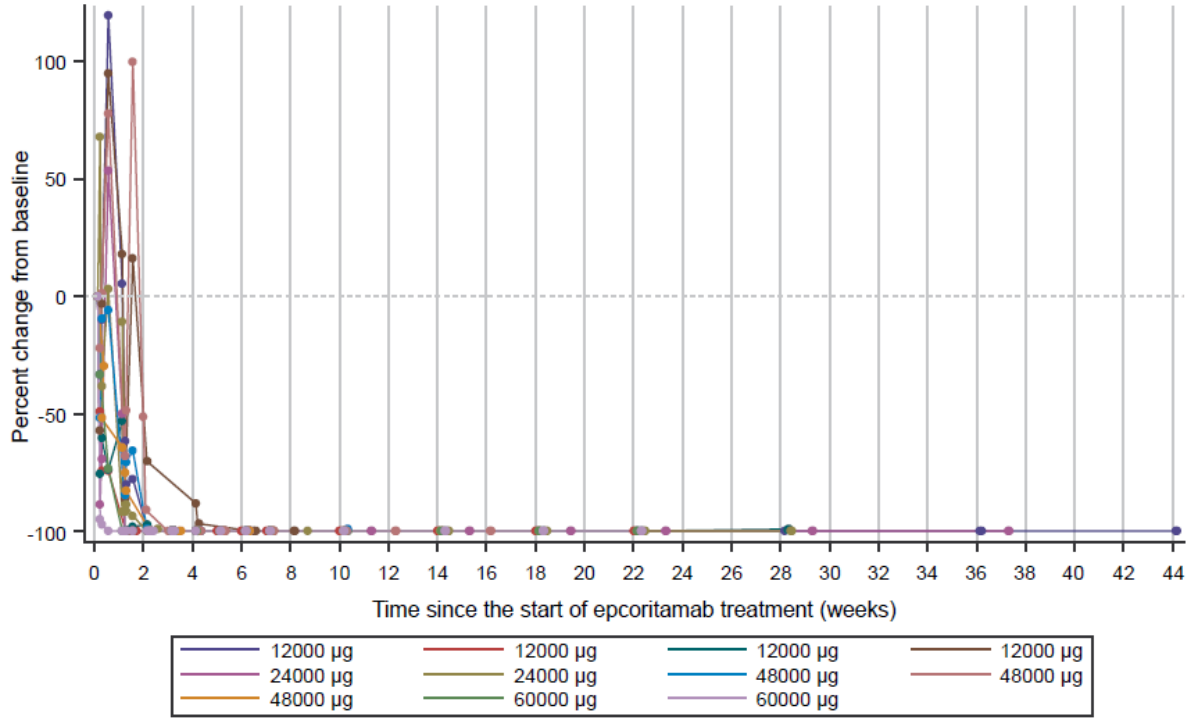
des one patient with MCL who died before post-baseline assessment.

des two patients with DLBCL; one patient died before receiving the first post-baseline evaluation and one patient did not have measurable disease ba scan evaluation at the time of enrollment.

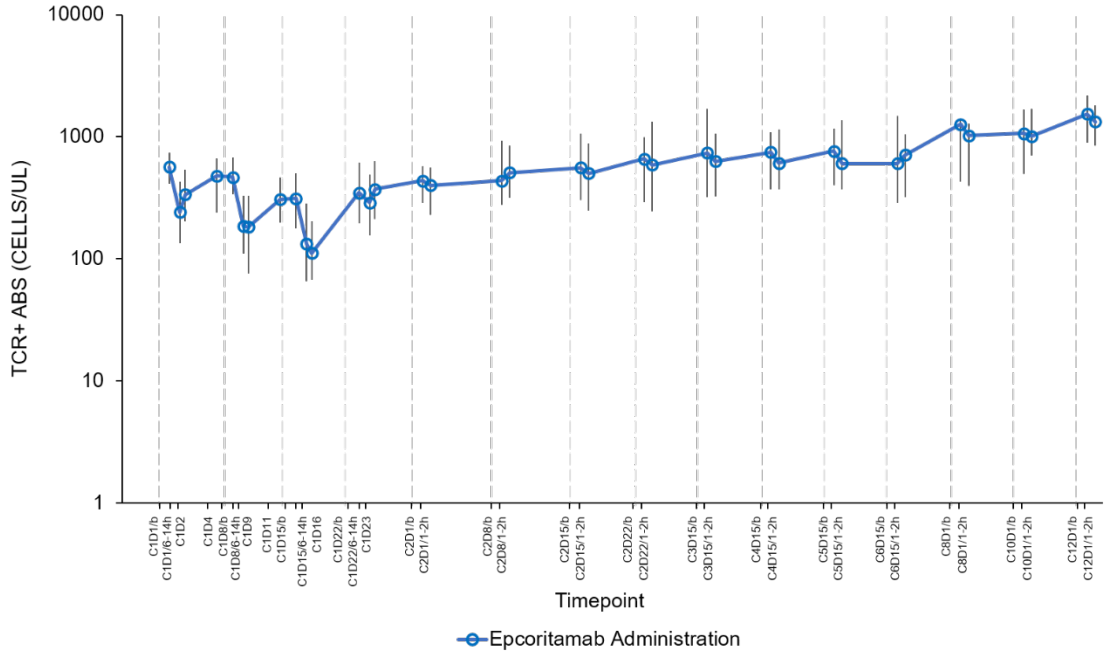
viations: CAR-T, chimeric antigen receptor T-cell therapy; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FDG, fluorodeoxygluco llicular lymphoma; MCL, mantle cell lymphoma; HSCT, hematopoietic stem cell transplantation; PD, progressive disease; PET, positron emission raphy; PFS, progression-free survival; PR, partial response; R/R, relapsed or refractory.

Figure 4. Changes in Immune Cell Populations and Cytokine Levels in Patients Treated With Epcoritamab

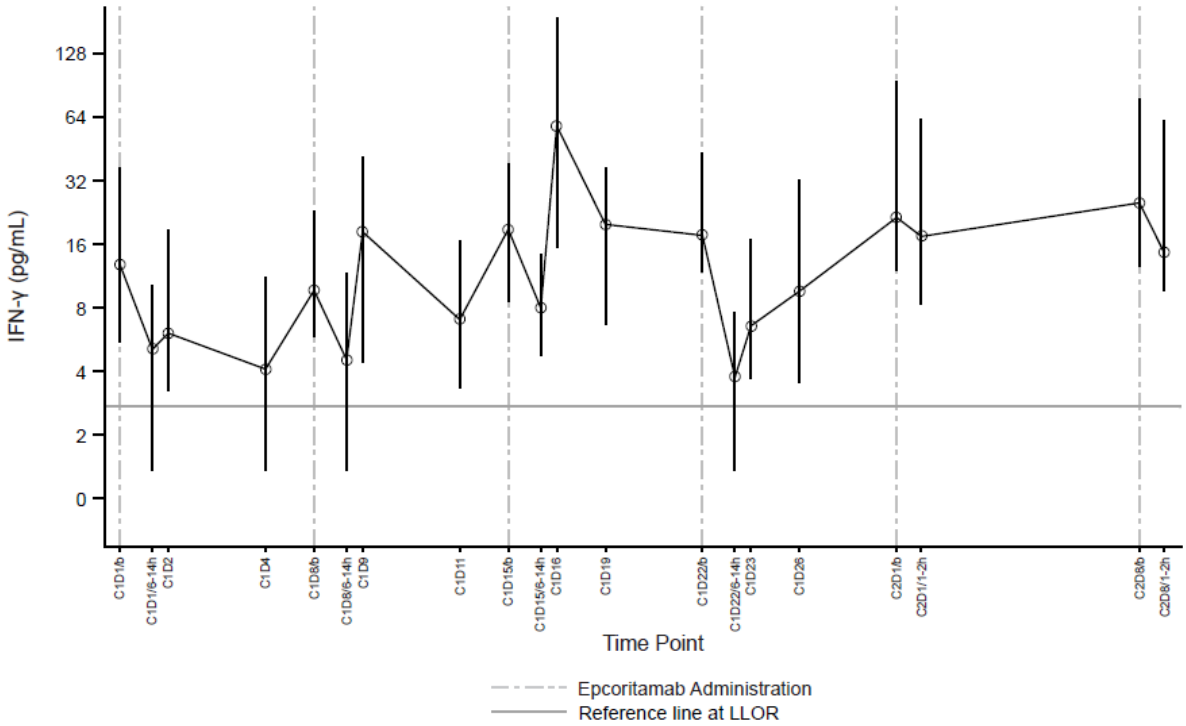
A. Change in Peripheral B-Cell Levels Over Time After Treatment With SC Epcoritamab



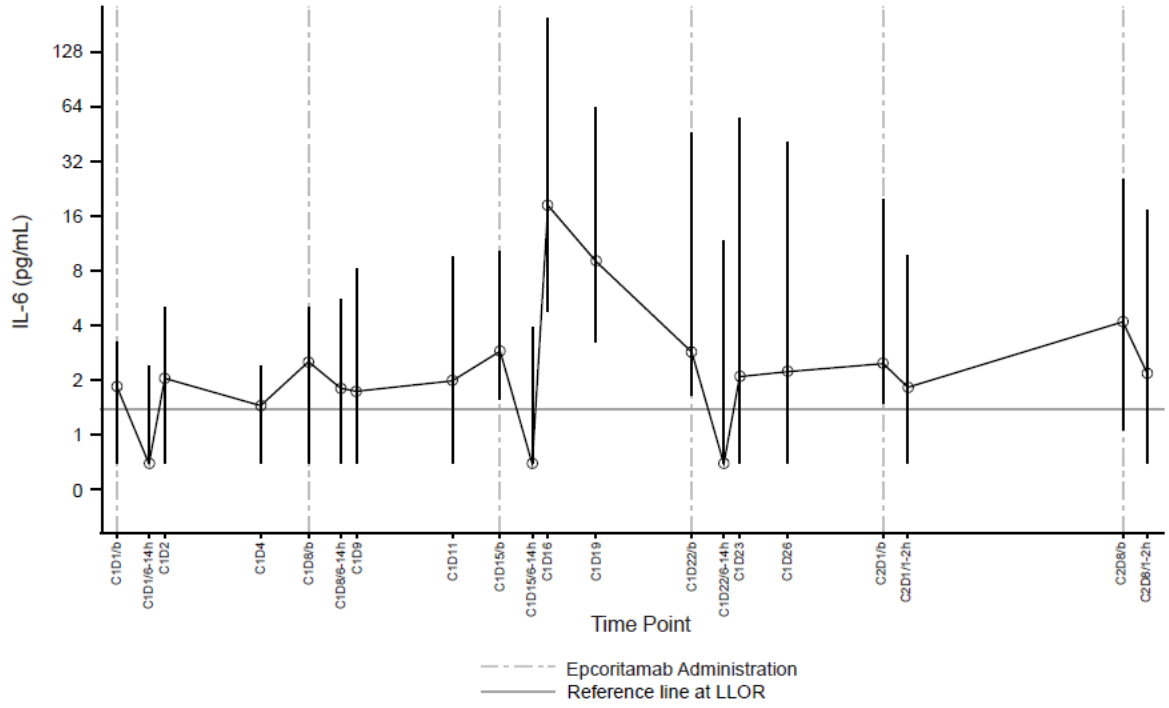
B. T-Cell Expansion in Peripheral Blood After Administration of SC Epcoritamab: All Patients ≥12 mg Epcoritamab



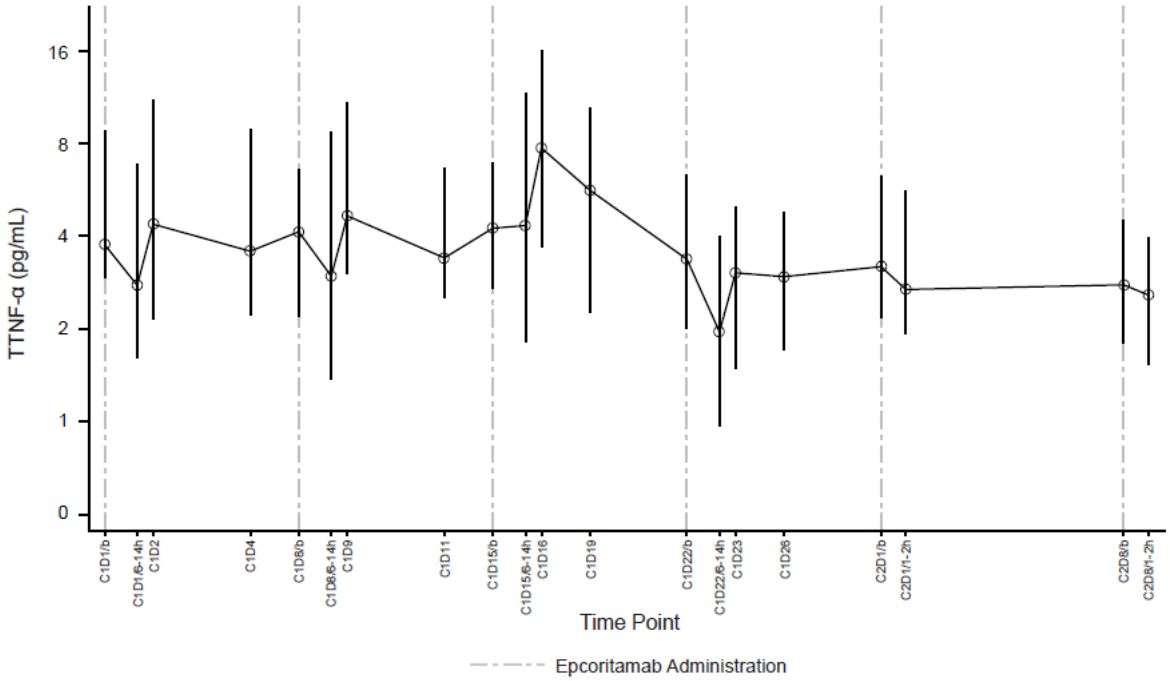
C. Longitudinal Change in Median Cytokine Levels After Administration of SC Epcoritamab: Interferon Gamma: All Patients ≥12 mg Epcoritamab



Interleukin 6: All Patients ≥12 mg Epcoritamab



Tumor Necrosis Factor Alpha: DLBCL ≥12 mg Epcoritamab



Data cut off October 19, 2020.
Median values are shown; error bars represent the interquartile range.
Colored lines in (A) represent individual patients.
Vertical dashed lines represent administration of epcoritamab.
Horizontal dashed lines represent the lower limit of reporting.
Abbreviations: DLBCL, diffuse large B-cell lymphoma; IFN-γ, interferon gamma; IL-6, interleukin 6; LLOR, lower limit of reporting; log, logarithm; SC, subcutaneous; TCR, T-cell receptor; TNF-α, tumor necrosis factor alpha.

APPENDIX TO:

Subcutaneous Epcoritamab in Patients With Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma: Results From a First-in-Human Phase 1 Dose-Escalation Study

Martin Hutchings[1], Rogier Mous[2], Michael Roost Clausen[3], Peter Johnson[4], Kim M. Linton[5], Martine E.D. Chamuleau[6], David John Lewis[7], Anna Sureda Balari[8], David Cunningham[9], Roberto S. Oliveri[10], Brian Elliott[11], Dena DeMarco[11], Ada Azaryan[11], Christopher Chiu[11], Tommy Li[11], Kuo-mei Chen[11], Tahamtan Ahmadi[11], Pieternella J. Lugtenburg[12]

[1]Rigshospitalet, Copenhagen, Denmark; [2]Lunenburg Lymphoma Phase I/II Consortium-HOVON/LLPC, Universitair Medisch Centrum Utrecht, Utrecht, Netherlands; [3]Vejle Hospital, Vejle, Denmark; [4]Cancer Research UK, Cancer Services, University of Southampton, Southampton, United Kingdom; [5]Manchester Cancer Research Centre, The Christie NHS Foundation Trust, The University of Manchester, Manchester, United Kingdom; [6]Lunenburg Lymphoma Phase I/II Consortium-HOVON/LLPC, VU University Medical Center, Amsterdam, Netherlands; [7]Plymouth University Medical School, Plymouth, United Kingdom; [8]Institut Català d'Oncologia-Hospital Duran i Reynals, Hospitalet del Llobregat, IDIBELL, Universitat de Barcelona, Spain; [9]The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; [10]Genmab A/S, Copenhagen, Denmark; [11]Genmab, Princeton, NJ; [12]Lunenburg Lymphoma Phase I/II Consortium-HOVON/LLPC, Erasmus MC Cancer Institute, Department of Hematology, Rotterdam, Netherlands.

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Rigshospitalet
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Pharmacokinetic (PK) analyses and PK/pharmacodynamic modeling

Plasma concentrations of epcoritamab were evaluated using blood samples obtained during Cycle 1 before treatment on Days 1, 8, 15, and 22 and at prespecified post-dose time points on Days 1-4, 8-11, 15, 16, 19, 22, 23, and 26. PK parameters (clearance, volume of distribution, area under the plasma concentration–time curve, maximum plasma concentration, time to reach maximum plasma concentration, and half-life) were calculated based on non-compartmental methods. Population PK analysis was performed using Monolix software (2019R2). Compartment PK model was fitted to clinical PK data and PK model parameters were estimated with good precision. Using the fitted population PK model, simulation was performed to assess PK dose proportionality. Simulations were performed with 100 virtual patients at each dose level. Simulations show that saturation of nonlinearity in PK occurs at epcoritamab doses ≥48 mg.

The PK/PD modeling approach incorporated a minimal physiologically based PK model to determine epcoritamab concentrations in tissues and lymph nodes, a binding model to evaluate target engagement and trimer formation, a T-cell activation model to assess T-cell expansion and cytotoxic killing of tumor cells, and a tumor dynamic model that incorporated baseline tumor size to predict clinical response. Clinical response data were used for PK/PD calibration. Exposure-response analysis was first conducted using an empirical E_{max} model. Following empirical exposure-response analysis, clinical trial simulations were conducted to calibrate prediction by the PK/PD model and obtain relevant model parameter values. Clinical trial simulations were conducted by repeatedly simulating (n=100) the design of the escalation phase of the trial. For each replica of the simulated escalation trial, patient PK parameters were fixed to individual post-hoc PK parameters estimated from fitting of the population PK model to clinical PK data. When available, patient-specific values were used for model parameters, based on clinical biomarker data and tumor size data (e.g., baseline T cell and B cell count, initial tumor size). When patient-specific values were not available, the value of model parameters associated with a specific patient was sampled from a distribution. After simulation of each replica trial, exposure-response analysis was conducted to fit the empirical E_{max} model to patient response in the simulated trial. Result from exposure-response analysis from all 100 replica trials were summarized and compared against results from the empirical exposure-response analysis performed on observed clinical response data. Values for select model parameters were adjusted iteratively until a best match between clinical trial simulation exposure-response and observed exposure-response was obtained.

Criteria for stopping dose escalation

Dose escalation was stopped if the maximum sample size had been reached; there were nine dose-limiting toxicity (DLT)–evaluable patients at the current dose level and the decision was to remain on the same dose level based on the dose-escalation rules; if the lowest dose was disallowed; or if there were six DLT–evaluable patients with ≤1 DLT on the current dose level provided that a higher dose level had already been evaluated, and the number of DLTs at the higher dose level had led to a de-escalation.

Ethics Approvals by Country

United Kingdom

Health Research Authority/Research Ethics Committee reference number: 18/SC/0303

Clinical Trial Authorisation/Medicine and Healthcare Products Regulatory Agency: 18645/0229/001

Denmark

De Videnskabsetiske Komiteer for Region Hovedstaden reference number: H-18047242

Netherlands

Medical Research Ethics Committee reference number: 2018-017

Table S1. Enrollment by Site

Investigator	Institution	Number of Patients Enrolled
Martin Hutchings	Copenhagen University Hospital, Copenhagen, Denmark	14
Michael Roost Clausen	Vejle Hospital, Vejle, Denmark	9
Rogier Mous	Lunenburg Lymphoma Phase I/II Consortium-HOVON/LLPC, Universitair Medisch Centrum Utrecht, Utrecht, Netherlands	9
Pieternella J Lugtenburg	Lunenburg Lymphoma Phase I/II Consortium-HOVON/LLPC, Erasmus MC Cancer Institute, Department of Hematology, Rotterdam, Netherlands.	7
Peter Johnson	Cancer Research UK, Cancer Services, University of Southampton, Southampton, United Kingdom	7
Kim M Linton	Manchester Cancer Research Centre, The Christie NHS Foundation Trust, The University of Manchester, Manchester, United Kingdom	6
David John Lewis	Plymouth University Medical School, Plymouth, United Kingdom	5
Martine Chamuleau	Lunenburg Lymphoma Phase I/II Consortium-HOVON/LLPC, VU University Medical Center, Amsterdam, Netherlands;	5

Anna Sureda Balari	Institut Català d'Oncologia-Hospital Duran i Reynals, Hospitalet del Llobregat, IDIBELL, Universitat de Barcelona, Spain	4
David Cunningham	The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom	2

Table S2. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Age ≥18 years and Eastern Cooperative Oncology Group performance status 0, 1, or 2	Primary central nervous system (CNS) lymphoma or known CNS involvement by lymphoma at screening as confirmed by magnetic resonance imaging/computed tomography scan (brain) and, if clinically indicated, by lumbar puncture
Documented CD20+ mature B-cell neoplasm according to World Health Organization classification: • Diffuse large B-cell lymphoma – de novo or transformed • High-grade B-cell lymphoma • Primary mediastinal large B-cell lymphoma • Follicular lymphoma • Mantle cell lymphoma • Small lymphocytic lymphoma • Marginal zone lymphoma (nodal, extra-nodal, or mucosa associated)	Known past or current malignancy other than inclusion diagnosis, except for: • Cervical carcinoma of Stage 1B or less • Non-invasive basal cell or squamous cell skin carcinoma • Non-invasive, superficial bladder cancer • Prostate cancer with a current PSA level <0.1 ng/mL • Any curable cancer with a complete response duration of >2 years
Relapsed, progressive and/or refractory disease following treatment with an anti-CD20 monoclonal antibody (e.g., rituximab), potentially in combination with chemotherapy and/or relapsed after autologous stem cell rescue • Patients must have exhausted or been ineligible for all standard therapeutic options • Patients with indolent lymphoma (follicular, marginal zone, or small lymphocytic lymphoma) must have a need for treatment initiation based on symptoms and/or disease burden	Known clinically significant cardiac disease, including: • Onset of unstable angina pectoris within 6 months of signing the informed consent form • Acute myocardial infarction within 6 months of signing the informed consent form • Congestive heart failure (grade III or IV as classified by the New York Heart Association) and/or known decrease ejection fraction of <45%
Documentation of CD20+ mature B-cell neoplasm based on any representative pathology report	AST and/or ALT >3x upper limit of normal; total bilirubin >1.5x upper limit of normal; creatinine clearance <45 mL/min
At least one measurable site of disease based on computed tomography (CT) (or magnetic resonance imaging [MRI]) with involvement of two or more clearly demarcated lesions/nodes with a long axis >1.5 cm and short axis >1.0 cm or one clearly demarcated lesion/node with a long axis >2.0 cm and short axis ≥ 1.0 cm AND baseline fluorodeoxyglucose positron emission tomography scans demonstrating positive lesion compatible with CT- or MRI-defined anatomical tumor sites	Chronic ongoing infectious diseases (except hepatitis B or hepatitis C) requiring treatment (excluding prophylactic treatment) at the time of enrolment or within the previous 2 weeks prior to the first dose of epcoritamab
Lymphocyte counts <5 x 10^9/L; platelet counts ≥75 x 10^9/L; absolute neutrophil counts ≥1.0 x 10^9/L; growth factor support allowed in case of bone marrow involvement	Confirmed history or current autoimmune disease or other diseases resulting in permanent immunosuppression or requiring permanent immunosuppressive therapy; low-dose prednisolone for rheumatoid arthritis or similar conditions is allowed
Hemoglobin level ≥9 g/dL (≥5.6 mmol/L) with or without transfusion	Seizure disorder requiring therapy (such as steroids or anti-epileptics)
At least 4 weeks from last dose of unconjugated anti-CD20 targeting therapy until first dose of epcoritamab	Any prior therapy with an investigational bispecific antibody targeting CD3 and CD20
At least 12 weeks from last dose of radio-conjugated or toxin-conjugated compound until first dose of epcoritamab	Prior treatment with chimeric antigen receptor T-cell therapy within 30 days prior to first administration of epcoritamab
At least 4 weeks from last dose of investigational monoclonal antibodies, investigational chemotherapy, or other investigational anti-cancer agent until first dose of epcoritamab	Patients eligible for curative intensive salvage therapy followed by high-dose chemotherapy with hematopoietic stem cell transplantation (HSCT) rescue
Resolution of toxicities from prior therapy to a grade that does not contraindicate trial participation in the opinion of the investigator	Autologous hematopoietic stem cell transplantation within 100 days prior to first administration of epcoritamab, or any prior allogeneic HSCT or solid organ transplantation

Inclusion Criteria	Exclusion Criteria
Before the first dose of epcoritamab, during the trial and for 12 months after last administration of epcoritamab, a woman must be either: • Not of childbearing potential*: premenarchal; postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle-stimulating hormone [FSH] level >40 IU/L or mIU/mL); permanently sterilized (e.g., bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations], hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy • Of childbearing potential and practicing a highly effective method of birth control (as defined by the European Union Clinical Trial Facilitation Group) consistent with local regulations regarding the use of birth control methods for patients participating in clinical trials: e.g., established use of oral, injected, or implanted combined (estradiol and progesterone-containing) hormonal contraception; placement of an intrauterine device or intrauterine system; male partner sterilization (the vasectomized partner should be the sole partner for that patient); true abstinence (when this is in line with the preferred and usual lifestyle of the patient *If the childbearing potential changes after start of the trial (e.g., woman who is not heterosexually active becomes active, premenarchal woman experiences menarche) a woman must begin a highly effective method of birth control	Active hepatitis B or hepatitis C (if laboratory evidence for a chronic infection with hepatitis B close monitoring and prophylactic therapy is required), or known human immunodeficiency virus infection
A man who is sexually active with a woman of childbearing potential must agree to use a barrier method of birth control (i.e, condom) during the trial and for 12 months after receiving the last dose of epcoritamab	Exposure to a live or a live attenuated vaccine within 4 weeks prior to signing the informed consent form
Women must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the trial and for 12 months after receiving the last dose of epcoritamab. Men must also not donate sperm during the trial and for 12 months after receiving the last dose of epcoritamab	Pregnancy or breast feeding
The patient understands the purpose of the trial and procedures required for the trial and is capable of providing signed informed consent as which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol	Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments
Each patient must sign a separate informed consent form if he or she agrees to provide sample(s) for evaluation of DNA. Refusal to give consent for the optional DNA research samples does not exclude a patient from participation in the dose-escalation part of the trial	Known hypersensitivity to allopurinol or rasburicase

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DNA, deoxyribonucleic acid.

Table S3. Epcoritamab Doses Administered by Cohort

Cohort	Cycle 1 doses in mg	Patients, n
1	0·004, 0·0128, 0·0128, 0·0128	1
2	0·0128, 0·04, 0·04, 0·04	2
3	0·04, 0·12, 0·12, 0·12	4
3a	0·04, 0·38, 0·38, 0·38	1
4	0·12, 0·38, 0·38, 0·38	1
5	0·04, 0·76, 0·76, 0·76	7
6	0·04, 0·25, 1·5, 1·5	5
7	0·04, 0·5, 3, 3	6
8	0·04, 0·5, 6, 6	7
8a	0·08, 0·5, 6, 6	2
9	0·04, 0·8, 12, 12	3
9a	0·08, 1·6, 12, 12	4
10	0·04, 0·8, 24, 24	6
10a	0·16, 0·8, 24, 24	4
11	0·08, 0·8, 48, 48	3
11a	0·16, 0·8, 48, 48	9
12	0·16, 0·8, 60, 60	3

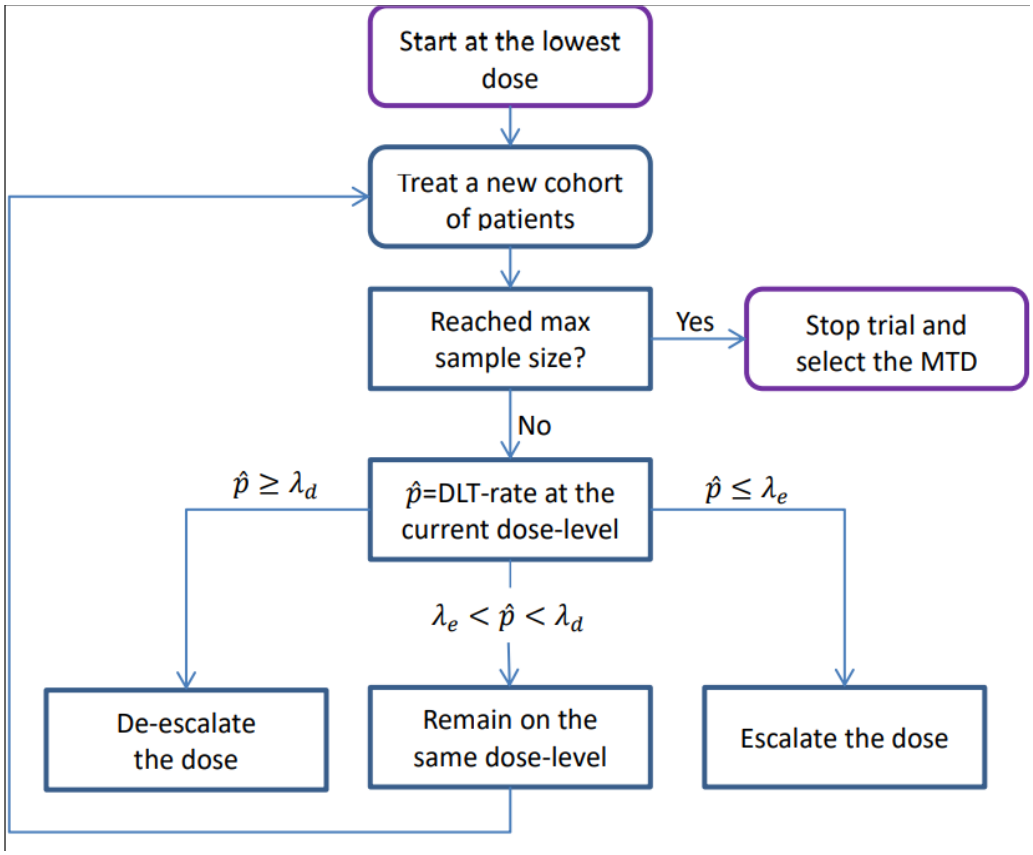
The last dose in Cycle 1 (i.e., full dose) is administered in Cycle 2 and subsequent cycles.
Cohorts ending in "a" were intended for parallel evaluation.

Table S4. Schedule of Assessment of Blood Samples for Pharmacokinetic Parameters, Immunophenotyping, Cytokine Levels, and Tumor Lysis Syndrome

Sampling Time Points	Cycle 1													
	1d	2d	3d	4d	8d	9d	10d	11d	15d	16d	19d	22d	23d	26d
Hospitalization visits														
Before epcoritamab administration	PK/C/I/ TLS				PK/C/I/ TLS				PK/C/I			PK/C/I		
+1 hours (±30 minutes) after epcoritamab administration	PK/TLS				PK/TLS				PK			PK		
+6-14 hours after epcoritamab administration	PK/C/I/ TLS				PK/C/I/ TLS				PK/C/I			PK/C/I		
+20-24 hours after epcoritamab administration		PK/C/I/ TLS				PK/C/I/ TLS				PK/C/I			PK/C/I	
+48 hours after epcoritamab administration (±4 hours)			PK/C/TLS				PK/C/TLS							
+72 hours after epcoritamab administration (±4 hours)				PK/C/I/ TLS				PK/C/I/ TLS						
Non-hospitalization visits														
											PK/C			PK/C

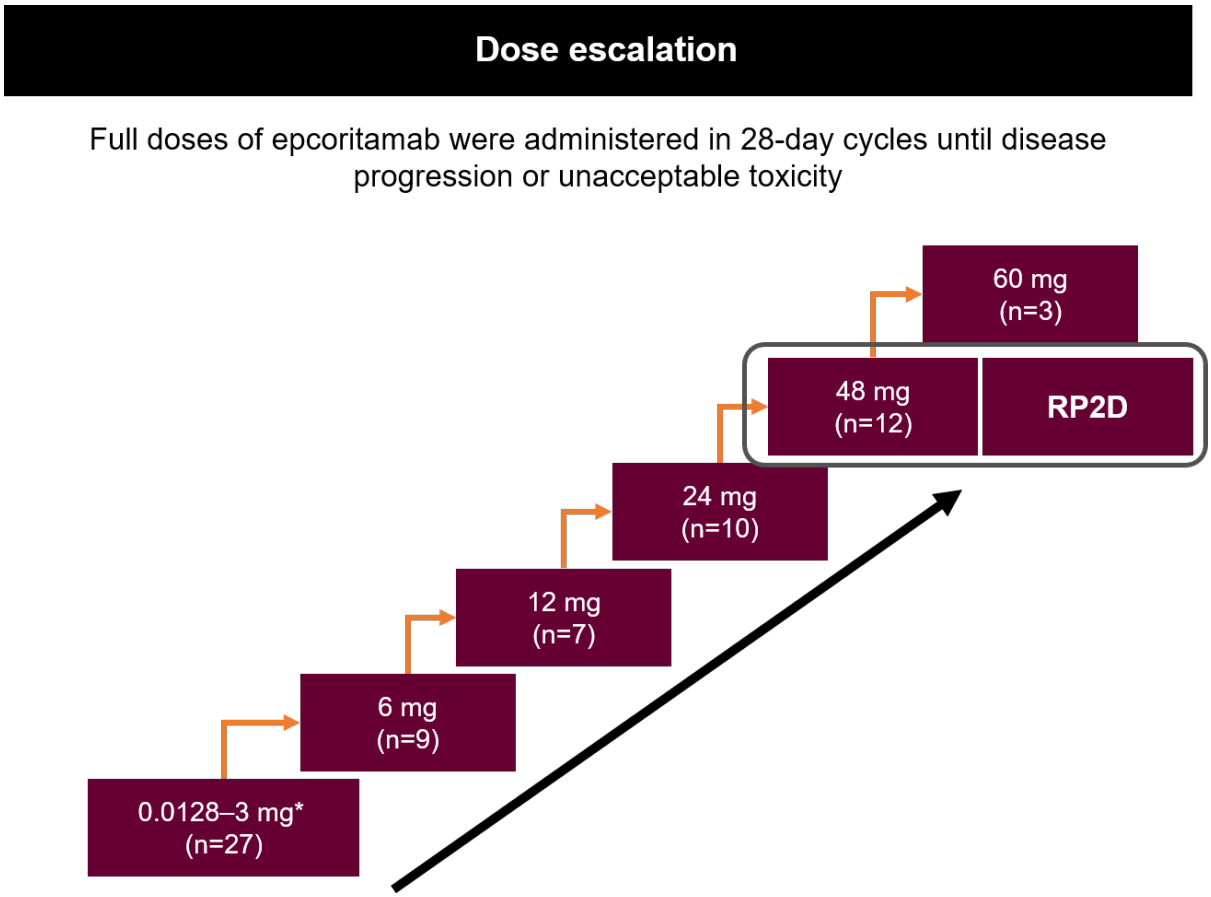
Abbreviations: C, cytokine evaluation; d, day; I, immunophenotyping by flow cytometry; PK, pharmacokinetic; TLS, tumor lysis syndrome.

Figure S1. Modified Bayesian Optimal Interval Design



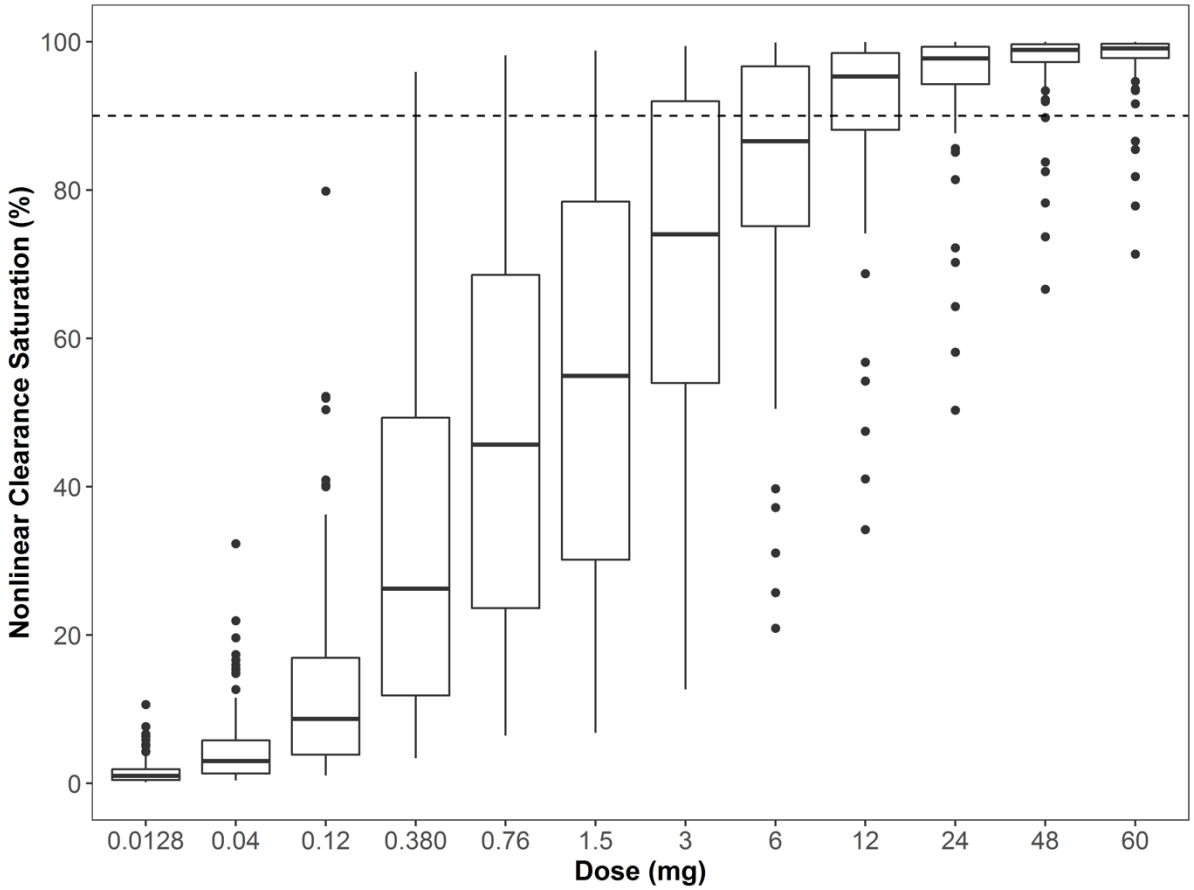
Abbreviations: DLT, dose-limiting toxicity; max, maximum; MTD, maximum tolerated dose.

Figure S2. Study Design



Dose escalation was performed using a modified Bayesian optimal interval design consisting of accelerated and standard titration. Accelerated titration includes single-patient cohorts; up to 2 patients could be added (at the currently investigated dose) to obtain additional pharmacokinetic/pharmacodynamic biomarker data.
*Includes the following priming/final dose levels (mg): 0·004/0·0128, 0·0128/0·04, 0·04/0·12, 0·12/0·38, 0·04/0·76, 0·04/0·25/1·5, 0·04/0·5/3.
Abbreviation: RP2D, recommended phase 2 dose.

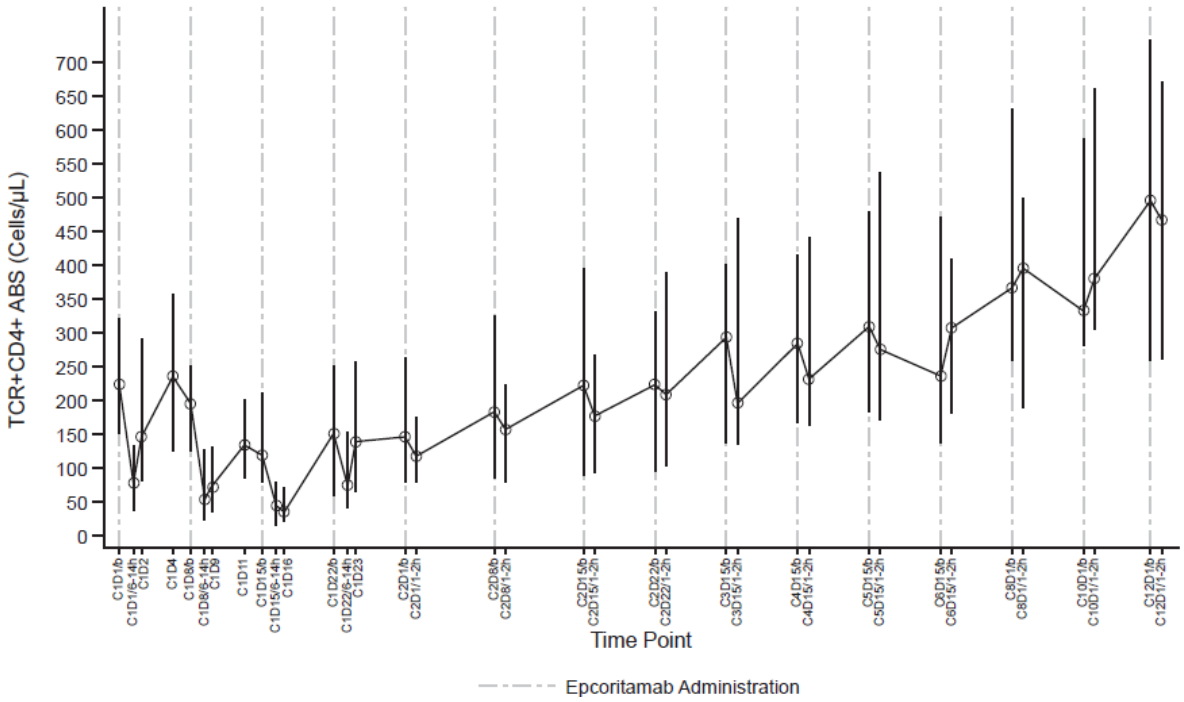
Figure S3. Non-linear Clearance Saturation by Epcoritamab Dose



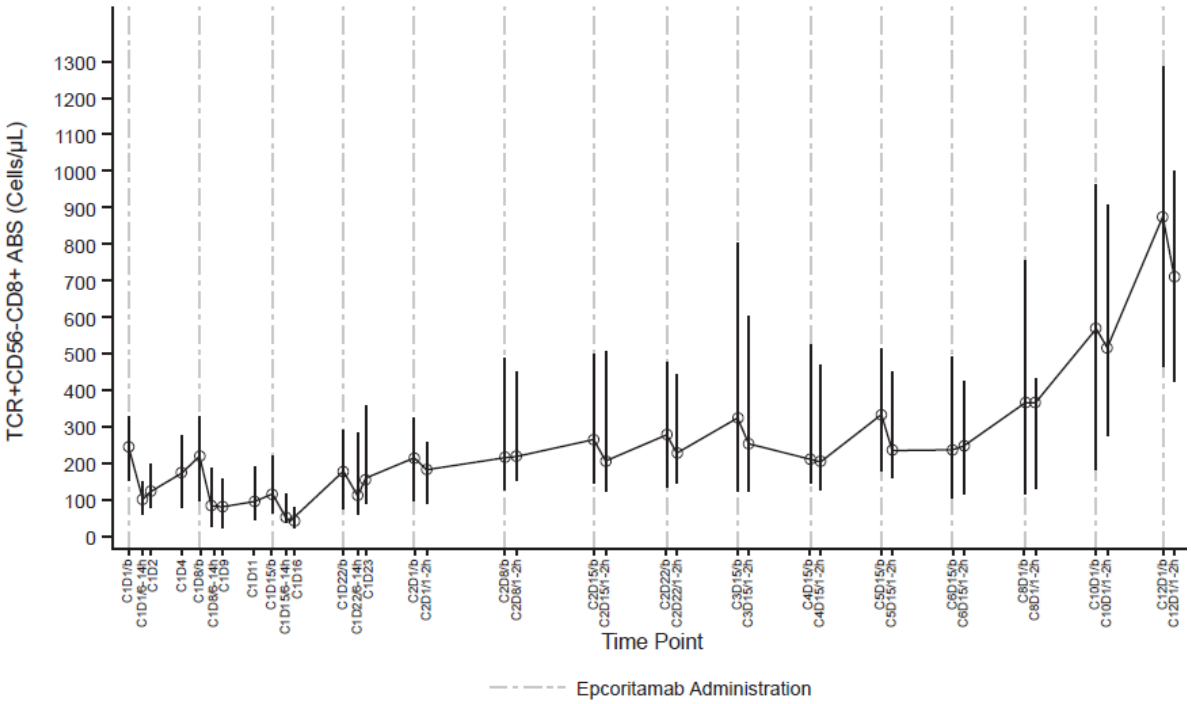
The population pharmacokinetics (PK) analysis was performed using Monolix software (2019R2). The compartmental PK model was fitted to clinical PK data and PK model parameters were estimated with good precision. Using the fitted population PK model, simulation was performed to assess PK dose proportionality. Simulations were conducted with 100 virtual patients at each dose level. The horizontal dashed line marks 90% saturation of nonlinear clearance. The simulations show that saturation of nonlinearity in PK occurs at epcoritamab doses ≥48 mg.

Figure S4. Change in the Numbers of CD4+ and T Cells After Administration of SC Epcoritamab

A. Change in the Number of CD4+ T Cells: All Patients ≥12 mg Epcoritamab



B. Change in the Number of CD56−/CD8+ T Cells: All Patients ≥12 mg Epcoritamab



Data cutoff October 19, 2020.
Median values are shown; error bars represent the interquartile range.
Abbreviations: ABS, absorption; DLBCL, diffuse large B-cell lymphoma; SC, subcutaneous; SD, standard deviation; TCR, T-cell receptor.