Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study

Lihua E Budde, Laurie H Sehn, Matthew Matasar, Stephen J Schuster, Sarit Assouline, Pratyush Giri, John Kuruvilla, Miguel Canales, Sascha Dietrich, Keith Fay, Matthew Ku, Loretta Nastoupil, Chan Yoon Cheah, Michael C Wei, Shen Yin, Chi-Chung Li, Huang Huang, Antonia Kwan, Elicia Penuel, Nancy L Bartlett

Summary

Background Mosunetuzumab is a CD20×CD3 T-cell-engaging bispecific monoclonal antibody that redirects T cells to eliminate malignant B cells. In a phase 1 study, mosunetuzumab was well tolerated and active in patients with relapsed or refractory B-cell lymphoma. We, therefore, aimed to evaluate the safety and anti-tumour activity of fixed-duration mosunetuzumab in patients with relapsed or refractory follicular lymphoma who had received two or more previous therapies.

Methods We conducted a single-arm, multicentre, phase 2 study at 49 centres in seven countries (Australia, Canada, Germany, South Korea, Spain, UK, and USA). All patients were aged 18 years or older with histologically confirmed follicular lymphoma (grade 1–3a) and an Eastern Cooperative Oncology Group performance status of 0–1. Patients had disease that was relapsed or refractory to two or more previous lines of treatment, including an anti-CD20 therapy and an alkylating agent. Intravenous mosunetuzumab was administered in 21-day cycles with cycle 1 step-up dosing: 1 mg on cycle 1 day 1, 2 mg on cycle 1 day 8, 60 mg on cycle 1 day 15 and cycle 2 day 1, and 30 mg on day 1 of cycle 3 and onwards. Patients with a complete response by investigator assessment using the International Harmonisation Project criteria completed treatment after cycle 8, whereas patients with a partial response or stable disease continued treatment for up to 17 cycles. The primary endpoint was independent review committee-assessed complete response rate (as best response) in all enrolled patients; the primary efficacy analysis compared the observed IRC-assessed complete response rate with a 14% historical control complete response rate in a similar patient population receiving the pan class I PI3K inhibitor copanlisib. Safety was assessed in all enrolled patients. This study is registered with ClinicalTrials.gov, number NCT02500407, and is ongoing.

Findings Between May 2, 2019, and Sept 25, 2020, we enrolled 90 patients. As of the data cutoff date (Aug 27, 2021), the median follow-up was 18·3 months (IQR 13·8–23·3). According to independent review committee assessment, a complete response was recorded in 54 patients (60·0% [95% CI 49·1–70·2]). The observed complete response rate was significantly higher than the historical control complete response rate with copanlisib of 14% (p<0·0001), thereby meeting the primary study endpoint. Cytokine release syndrome was the most common adverse event (40 [44%] of 90 patients) and was predominantly grade 1 (23 [26%] of 90) and grade 2 (15 [17%]), and primarily confined to cycle 1. The most common grade 3–4 adverse events were neutropenia or neutrophil count decreased (24 [27%] of 90 patients), hypophosphataemia (15 [17%]), hyperglycaemia (seven [8%]), and anaemia (seven [8%]). Serious adverse events occurred in 42 (47%) of 90 patients. No treatment-related grade 5 (ie, fatal) adverse event occurred.

Interpretation Fixed-duration mosunetuzumab has a favourable safety profile and induces high rates of complete remissions, allowing potential administration as an outpatient regimen, in patients with relapsed or refractory follicular lymphoma and two or more previous therapies.

Funding F Hoffmann-La Roche and Genentech.

Introduction

Follicular lymphoma is the second most common lymphoma worldwide. The course of this cancer is often characterised by relapsing disease, increasing refractoriness to anti-CD20 antibodies and chemotherapy, and decreasing survival rates with each subsequent therapy.[1–4] Patients with refractory or early relapsing disease can have an especially poor prognosis.[5,6] Effective new therapies with novel mechanisms of action are needed to overcome treatment resistance and improve outcomes for patients with late-line relapsed or refractory follicular lymphoma.

Mosunetuzumab is a full-length, IgG1-based CD20×CD3 T-cell engaging bispecific monoclonal antibody that engages and redirects T cells to eliminate malignant B cells.[7] An international phase 1/2 study (NCT02500407)

Lancet Oncol 2022

Published Online July 5, 2022 https://doi.org/10.1016/S1470-2045(22)00335-7

See Online/Comment https://doi.org/10.1016/S1470-2045(22)00385-0

Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA, USA (L E Budde MD); **Department of Medical Oncology, BC Cancer Centre for Lymphoid Cancer, Vancouver, BC, Canada** (L H Sehn MD); **Department of Medicine, The University of British Columbia, Vancouver, BC, Canada** (L H Sehn); **Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA** (M Matasar MD); **Lymphoma Translational Research, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA** (S J Schuster MD); **Division of Hematology, Jewish General Hospital, Montreal, QC, Canada** (S Assouline MD); **Department of Haematology, Royal Adelaide Hospital, Adelaide, SA, Australia** (P Giri MBBS); **Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada** (J Kuruvilla MD); **Servicio de Hematología, Hospital Universitario La Paz, Madrid, Spain** (M Canales MD); **Department of Internal Medicine V: Hematology, Oncology and Rheumatology, Heidelberg University, Heidelberg, Germany** (S Dietrich MD); **Department of Haematology, Royal North Shore Hospital, Sydney, NSW, Australia** (K Fay MBChB); **Department of Haematology, St Vincent's Hospital, University of Melbourne,**

Melbourne, VIC, Australia (M Ku MBBS, K Fay); **Department of Lymphoma/Myeloma, MD Anderson Cancer Center, Houston, TX, USA** (L Nastoupil MD); **Linear Clinical Research, Sir Charles Gairdner Hospital, Perth, WA, Australia** (C Y Cheah MBBS); **Department of Haematology, The University of Western Australia, Perth, WA, Australia** (C Y Cheah); **Genentech, San Francisco, CA, USA** (M C Wei MD, S Yin PhD, C-C Li PhD, A Kwan MBBS, E Penuel PhD); **F Hoffmann-La Roche, Mississauga, ON, Canada** (H Huang MSc); **Division of Oncology, Siteman Cancer Center, Washington University School of Medicine, St Louis, MO, USA** (Prof N L Bartlett MD)

Correspondence to: Prof Nancy L Bartlett, Division of Oncology, Siteman Cancer Center, Washington University School of Medicine, St Louis, MO 63110, USA
nbartlet@wustl.edu

Research in context

Evidence before this study

We searched PubMed on Feb 4, 2022, for articles published in the past 10 years containing combinations of the following terms or phrases in the title or abstract only: "(relapsed OR refractory) AND (indolent lymphoma OR indolent non-Hodgkin lymphoma OR follicular lymphoma) AND (two or more OR at least 2 OR ≥2) AND (lines of therapy / treatment OR prior therapies / treatments OR previous therapies / treatments OR therapy / treatment lines OR systemic therapies / treatments) AND (Phase II OR Phase 2 OR Phase III OR Phase 3)". Review articles and editorials (or similar) were excluded. We identified ten publications on clinical studies investigating the safety and efficacy of Bruton's tyrosine kinase, PD-1, PI3K, and EZH2 inhibitors and chimeric antigen receptor (CAR) T-cell therapies in patients with relapsed or refractory indolent non-Hodgkin lymphoma or follicular lymphoma who had received two or more previous lines of therapy. As a result of these studies, four PI3K inhibitors (idelalisib, copanlisib, duvelisib, and umbralisib), one EZH2 inhibitor (tazemetostat), and one CAR T-cell therapy (axicabtagene ciloleucel) have been approved for clinical use in patients with relapsed or refractory follicular lymphoma and two or more previous lines of therapy in the USA and in Europe, although recently the sponsors of idelalisib and duvelisib have voluntarily withdrawn the accelerated approval of these agents for relapsed or refractory follicular lymphoma in the USA. In the supporting pivotal studies of the approved PI3K and EZH2 inhibitors, objective response rates were reasonably high in the primary analyses (42–69%), but complete response rates were low (1–14%) and the duration of response was relatively short (median ≤12 months in patients with relapsed or refractory follicular lymphoma or indolent non-Hodgkin lymphoma). In the corresponding pivotal study of the approved CAR T-cell therapy, response rates were high (objective response rate of 94% and complete response rate of 79%) and the median duration of response was not reached at data cutoff, although early adverse events, such as high-grade cytokine release syndrome and neurological adverse events, were also reported. Complex procedures and an extended manufacturing lead time were noted. In addition to the above therapies approved for relapsed or refractory follicular lymphoma and two or more previous lines of therapy, other therapies approved in earlier lines such as obinutuzumab plus bendamustine or rituximab plus lenalidomide might be used, noting that non-cross-resistant regimens are preferred for patients with early relapse.

Added value of this study

Mosunetuzumab is a T-cell engaging CD20 × CD3 bispecific monoclonal antibody that is in development as an off-the-shelf immunotherapy for the treatment of relapsed or refractory non-Hodgkin lymphoma. To our knowledge, this study is the first to report positive data from a phase 2 expansion for a CD20 × CD3 bispecific antibody in patients with relapsed or refractory follicular lymphoma and is also the largest dataset in such patients. A high rate of durable responses was observed in the overall patient population, which was heavily pretreated. With a fixed duration of treatment, more than half of all responders had ongoing responses at 18 months after the first response. In subgroup analyses, consistent response rates were observed among patients who had high-risk disease characteristics. In addition, mosunetuzumab demonstrated a favourable safety profile, with a low rate of treatment discontinuation. Step-up dosing in the first cycle provided effective cytokine release syndrome mitigation, allowing administration as an outpatient regimen.

Implications of all the available evidence

Mosunetuzumab represents an active and well tolerated treatment option for patients with relapsed or refractory follicular lymphoma and two or more previous therapies that appears to be an advance in terms of anticancer activity, safety, and accessibility over the currently available therapies, although no head-to-head studies exist. Several other CD20 × CD3 bispecific antibodies are in clinical development, although pivotal data in relapsed or refractory follicular lymphoma for such agents are not yet available. The overall benefit-to-risk ratio of mosunetuzumab in patients with relapsed or refractory follicular lymphoma and two or more previous therapies appears favourable and will be further validated in ongoing studies, including a phase 3 trial comparing mosunetuzumab plus lenalidomide with rituximab plus lenalidomide in patients with relapsed or refractory follicular lymphoma and one or more previous therapy (NCT04712097).

is evaluating the safety and efficacy of fixed-duration mosunetuzumab in patients with relapsed or refractory B-cell lymphoma.[8] In a phase 1 study, escalating intravenous mosunetuzumab doses showed a favourable safety profile, with cycle 1 step-up dosing providing effective mitigation of cytokine release syndrome.[9] High complete response rates and durable remissions were observed in patients with relapsed or refractory follicular lymphoma with two or more previous lines of therapy, including those with a history of progression of disease within 24 months from the start of initial therapy.[9] The recommended phase 2 dosing schedule for intravenous mosunetuzumab in relapsed or refractory B-cell lymphoma was also previously defined.[8]

Given these encouraging results, we aimed to evaluate the safety and anticancer activity of fixed-duration mosunetuzumab in patients with relapsed or refractory follicular lymphoma who had received two or more previous lines of therapy.

Methods

Study design and participants

We conducted a single-arm, multicentre, phase 2 study at 49 centres in seven countries (Australia, Canada,

Germany, South Korea, Spain, UK, and USA). All patients were aged 18 years or older with histologically confirmed follicular lymphoma (grade 1–3a) and an Eastern Cooperative Oncology Group performance status of 0–1. Patients had disease relapsed or refractory to two or more previous lines of treatment, including an anti-CD20 therapy and an alkylating agent. Full eligibility criteria are summarised in the appendix (pp 4–5).

The study protocol was approved by institutional review boards at each centre. The trial was done in accordance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable laws and regulations. We obtained written informed consent from all eligible patients.

Procedures

Intravenous mosunetuzumab was administered in 21-day cycles with cycle 1 consisting of step-up dosing: 1 mg on cycle 1 day 1, 2 mg on cycle 1 day 8, 60 mg on cycle 1 day 15 and cycle 2 day 1, and 30 mg on day 1 of cycle 3 and onwards. Corticosteroid premedication (dexamethasone 20 mg or methylprednisolone 80 mg) was given intravenously 1 h before each mosunetuzumab dose in cycles 1 and 2, and was optional from cycle 3 onwards. Admission to hospital for monitoring following mosunetuzumab infusion was not mandatory. Dose delays and dose modifications were allowed for the management of adverse events; details are included in the study protocol (appendix).

CT and PET-CT scans were done at screening and then at 6 weeks (optional), 3 months, and once every 3 months thereafter during treatment. During post-treatment follow-up, CT with or without PET scans were done once every 3 months during the first 18 months of the study, at 24 months, and then once every 12 months thereafter until disease progression, start of new anti-cancer therapy, or study discontinuation. Response was evaluated by independent review committee (IRC) assessment and investigator assessment of the CT or PET-CT scans using the International Harmonization Project response criteria.[10] A bone marrow examination was done at baseline and was required to be repeated to confirm complete response (within 42 days of radiographic complete response) if the bone marrow showed involvement by lymphoma at baseline. Patients with no response assessments were classified as non-responders. Patients who reached a complete response completed treatment after cycle 8. Patients who reached a partial response or had stable disease after cycle 8 continued treatment for up to 17 cycles. Re-treatment was allowed in complete responders who progressed after completion of initial treatment. Details of methods used in biomarker analyses are described in appendix p 5.

After the initiation of mosunetuzumab, adverse events were monitored until 90 days after the last dose of study drug or the initiation of another anti-cancer agent. Thereafter, serious adverse events related to the study treatment were monitored until study discontinuation. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria Adverse Events (version 4.0). Cytokine release syndrome was graded using the American Society for Transplantation and Cellular Therapy criteria.[11]

See Online for appendix

Outcomes

The primary efficacy endpoint was IRC-assessed complete response (as best response) rate in all enrolled patients. Secondary efficacy endpoints were investigator-assessed complete response rate, IRC and investigator-assessed objective response rate (complete response or partial response), IRC and investigator-assessed duration of response in responders and complete responders (defined as the time from initial occurrence of a partial or complete response to first progressive disease or death from any cause in all responders and in patients who achieved a complete response), IRC and investigator-assessed duration of complete response (defined as the time from initial occurrence of a complete response to first progressive disease or death from any cause), IRC and investigator-assessed progression-free survival (defined as time from first dose of mosunetuzumab to first progressive disease or death from any cause), and overall survival (defined as time from first dose of mosunetuzumab to death from any cause). Time to next treatment (defined as the time from end of mosunetuzumab treatment to the start of new anti-lymphoma therapy or death from any cause) was an exploratory efficacy endpoint. Detailed definitions of efficacy endpoints are included in the appendix (pp 5–6).

Safety and tolerability were assessed by the incidence, nature, and severity of adverse events, and by changes in laboratory parameters in all patients. Death due to progression of disease was captured as an adverse event in this study.

Statistical analysis

At the time of study initiation, the PI3K inhibitors idelalisib and copanlisib were the only approved agents for the treatment of relapsed or refractory follicular lymphoma after two or more previous lines of therapy. Therefore, the primary efficacy analysis aimed to test the observed IRC-assessed complete response rate in the intention-to-treat population versus the prespecified 14% historical control complete response rate, which was reported in the phase 2 study of copanlisib.[12] The exact binomial test was used to test the null hypothesis that the IRC-assessed complete response rate would be the same as the historical control, at a two-sided α level of 5%. The sample size of 90 patients would provide a power of more than 90% to detect a 14% increase in the complete response rate versus the historical control. The primary analysis was specified for approximately 6 months after the last patient received the first dose of mosunetuzumab.

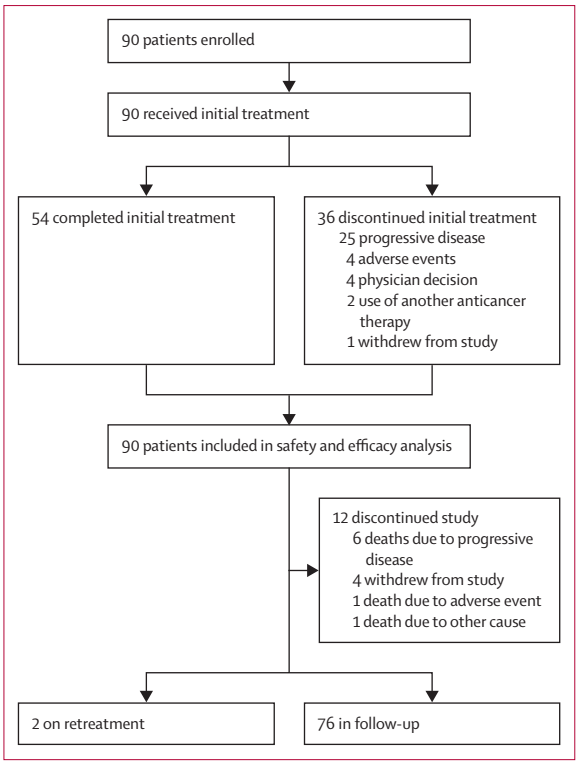

Figure 1: **Trial profile**

All enrolled patients were included in both the efficacy and safety analyses. The 95% CI of the IRC-assessed complete response rate was calculated using the Clopper-Pearson method.

For the secondary and exploratory efficacy endpoints, the Clopper-Pearson method was used to calculate the 95% CIs for the complete response and objective response rates. For duration of response in responders and complete responders, duration of complete response, progression-free survival, overall survival, and time to next treatment, the Kaplan-Meier method was used to estimate the medians and event-free rates at 12 months (ie, prespecified analysis) and 18 months (ie, post-hoc analysis). The Brookmeyer-Crowley method was used to calculate the 95% CIs for the medians, and the Greenwood's formula was used to calculate the 95% CIs for the event-free rates at 12 and 18 months.

Exploratory analyses were prespecified for objective response rate and complete response rate in patient subgroups. These subgroups are listed in the appendix (p 418). Post-hoc analyses were done to assess the time to first response and the time to first complete response per IRC and investigator assessment. Analyses on safety and adverse events were done descriptively. Post-hoc subgroup analyses on adverse events based on age (≤65 years, >65 years, and >70 years) and tumour burden (above or below the median) were performed descriptively. Post-hoc biomarker analyses were performed to examine potential associations between CD20 expression, peripheral

	All enrolled patients (n=90)
Age, years	60 (53–67)
Sex	
Male	55 (61%)
Female	35 (39%)
Ethnicity	
White	74 (82%)
Asian	8 (9%)
Black or African American	4 (4%)
American Indian or Alaska native	1 (1%)
Unknown	3 (3%)
ECOG performance status at study entry	
0	53 (59%)
1	37 (41%)
Ann Arbor stage at study entry	
I	5 (6%)
II	16 (18%)
III	25 (28%)
IV	44 (49%)
Bulky disease (>6 cm) at study entry	31 (34%)
FLIPI risk factors at study entry*	
0	3 (3%)
1	23 (26%)
2	24 (27%)
3	21 (23%)
4	18 (20%)
5	1 (1%)
Number of previous lines of therapy	3 (2–4)
Two previous lines	34 (38%)
Three previous lines	28 (31%)
More than three previous lines	28 (31%)
Previous lymphoma therapy	
Alkylator therapy	90 (100%)
Anti-CD20 therapy	90 (100%)
Immunochemotherapy (anti-CD20 plus alkylator or anthracycline)	88 (98%)
Anthracyclines	74 (82%)
PI3K inhibitors	17 (19%)
Immunomodulatory drugs	13 (14%)
Chimeric antigen receptor T-cell therapy	3 (3%)
Previous autologous stem cell transplant	19 (21%)
Refractory to last previous therapy	62 (69%)
Refractory to any previous anti-CD20 therapy	71 (79%)
Refractory to any previous anti-CD20 therapy and an alkylator therapy (double refractory)	48 (53%)
POD24	47 (52%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. FLIPI=Follicular Lymphoma International Prognostic Index. POD24=progression of disease within 24 months from the start of initial therapy. *The prognostic value of the FLIPI score was established in patients with newly diagnosed follicular lymphoma. The FLIPI score has not been validated in the relapsed or refractory setting, but has been shown to be associated with response and survival outcomes.[13]

Table 1: **Baseline patient and disease characteristics**

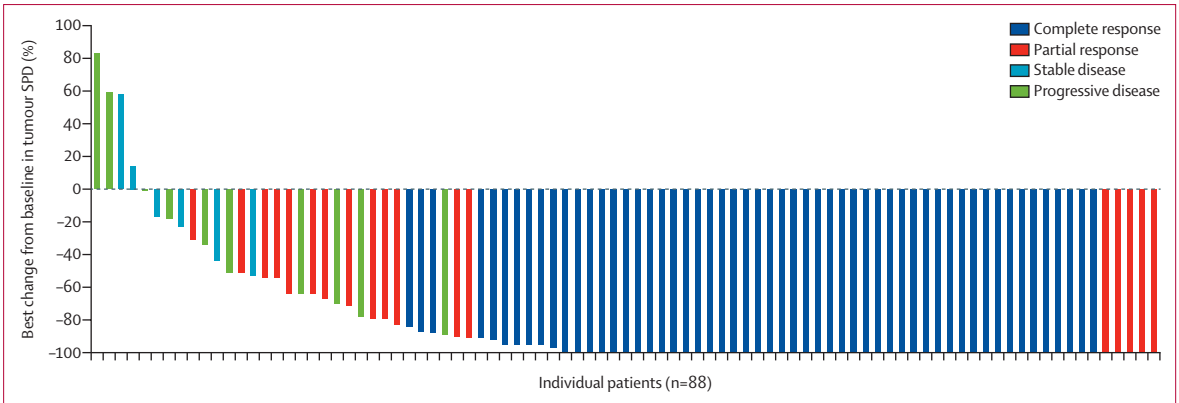

Figure 2: **Waterfall plot of best percentage change in SPD**
SPD=sum of the products of diameters.

immune cell counts, and *EZH2* mutation status at baseline and response.

We did all statistical analyses using SAS (version 9.4). This study is registered with ClinicalTrials.gov, number NCT02500407.

Role of the funding source

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

Results

Between May 2, 2019, and Sept 25, 2020, we enrolled 90 patients; 55 (61%) were men, and 69 (77%) had stage III–IV disease (figure 1; table 1). The median number of previous lines of therapy was three (IQR 2–4). All patients had received anti-CD20 therapies and alkylating agents before study entry (table 1). Overall, 62 (69%) of 90 patients were refractory to their last previous therapy, 71 (79%) were refractory to any previous anti-CD20 therapy, and 48 (53%) were double refractory to both previous anti-CD20 therapy and a previous alkylating agent. 47 (52%) of 90 patients had a history of progression of disease within 24 months from the start of initial therapy.

As of the data cutoff date (Aug 27, 2021), the median follow-up was 18·3 months (IQR 13·8–23·3). The median number of cycles of mosunetuzumab received was eight (IQR 8–8; appendix p 7). 54 (60%) of 90 patients had completed initial treatment and 36 (40%) patients had discontinued initial treatment prematurely due to progressive disease (25 [28%] of 90), adverse events (four [4%]), physician decision (four [4%]), use of another anti-lymphoma therapy (two [2%]), and patient withdrawal (one [1%]; figure 1). As of data cut-off, two (2%) of 90 patients were on retreatment, 76 (84%) were in follow-up, and 12 (13%) had discontinued the study.

Reduction in tumour size was observed in 84 (95%) of 88 evaluable patients with post-treatment imaging assessment available (figure 2). The proportion of patients who achieved an objective response according to IRC assessment was 80·0% (95% CI 70·3–87·7; 72 of 90 patients) and the proportion with a complete response was 60·0% (49·1–70·2; 54 of 90 patients). All complete responses were confirmed by PET and bone marrow examination (if bone marrow was involved at baseline). The primary efficacy endpoint was met ($p<0·0001$ *vs* the 14% historical control complete response rate with copanlisib) at the prespecified primary analysis. The objective response and complete response rates by investigator assessment were highly concordant with those by IRC assessment (table 2).

The objective response rate and complete response rate assessed by IRC in prespecified patient subgroups are shown in the appendix (p 12); responses were observed in all patient subgroups, including those with high-risk disease. Activity was also observed in eight patients with disease harbouring EZH2 mutations (assessed by whole exome sequencing; six responders, including three complete responses).

Time to first response and to first complete response per IRC assessment and investigator are shown in table 2. Among 16 patients who received treatment beyond eight cycles (up to a maximum of 17 cycles), a late initial response or deepening of initial response was observed in six (38%) patients, including five (31%) patients who achieved complete response after receiving more than eight cycles.

According to IRC assessment, median progression-free survival was 17·9 months (95% CI 10·1–not reached; figure 3A); 12-month and 18-month progression-free survival by IRC and investigator assessment are shown in table 2. Median duration of response per IRC was 22·8 months (95% CI 9·7–not reached); although it should be noted that only four patients remained at risk by month 22 and the estimated median might not be robust (figure 3B). Based on the Kaplan-Meier estimation, 56·9% (95% CI 44·1–69·6) of all responders (figure 3B) and 70·2% (56·7–83·8) of complete responders (table 2; appendix p 13) maintained their responses for at least 18 months. The median duration of complete response

	Independent review committee assessment (n=90)	Investigator assessment (n=90)
Objective response rate*	72 (80·0% [70·3–87·7])	70 (77·8% [67·8–85·9])
Complete response rate*	54 (60·0% [49·1–70·2])	54 (60·0% [49·1–70·2])
Time to first response, months	1·4 (1·2–2·9)	1·4 (1·2–2·8)
Time to first complete response, months	3·0 (1·4–5·7)	3·0 (1·4–5·7)
Duration of response		
Patients with event	29/72 (40%)	27/70 (39%)
Median, months (95% CI)	22·8† (9·7–NR)	22·8† (18·7–NR)
12-month event-free rate	61·8% (50·0–73·7)	64·8% (53·1–76·5)
18-month event-free rate	56·9% (44·1–69·6)	62·5% (50·4–74·7)
Duration of response in complete responders		
Patients with event	16/54 (30%)	12/54 (22%)
Median, months (95% CI)	22·8† (18·7–NR)	22·8† (19·9–NR)
12-month event-free rate	76·4% (64·6–88·1)	84·3% (74·3–94·3)
18-month event-free rate	70·2% (56·7–83·8)	81·3% (70·0–92·5)
Duration of complete response		
Patients with event	16/54 (30%)	12/54 (22%)
Median, months (95% CI)	NR (14·6–NR)	NR (17·8–NR)
12-month event-free rate	71·4% (57·9–84·9)	80·4% (68·8–92·0)
18-month event-free rate	63·7% (48·0–79·4)	66·6% (45·5–87·8)
Progression-free survival		
Patients with event	42 (47%)	41 (46%)
Median, months (95% CI)	17·9 (10·1–NR)	21·1 (11·8–NR)
12-month event-free rate	57·7% (46·9–68·4)	57·6% (46·8–68·4)
18-month event-free rate	47·0% (34·4–59·6)	51·0% (38·9–63·0)
Time to next treatment‡		
Patients with event	NA	33 (37%)
Median, months (95% CI)	NA	NR (16·2–NR)
12-month event-free rate	NA	68·1% (58·3–77·9)
18-month event-free rate	NA	61·0% (50·0–72·0)
Overall survival‡		
Patients with event	NA	8 (9%)
Median, months (95% CI)	NA	NR (NR–NR)
12-month event-free rate	NA	93·0% (87·6–98·4)
18-month event-free rate	NA	89·6% (82·5–96·6)

Data are n (% [95% CI]), median (IQR), n (%), or n/N (%), unless otherwise specified. NR=not reached. *Best response. †The estimate of the median was based on less than 10% of responders remaining at risk and might not be robust. ‡Time to next treatment and overall survival are objective (ie based on date of death or next line of treatment) and therefore did not require assessment by independent review committee or investigator.

Table 2: **Efficacy summary in all patients**

per IRC was not reached (95% CI 14·6 to not reached; figure 3C). The median time to next treatment and median overall survival were not reached (table 2); estimated event-free rates at 18 months were 61·0% (95% CI 50·0–72·0) for time to next treatment and 89·6% (82·5–96·6) for overall survival (table 2; appendix p 14).

Target CD20 expression by immunohistochemistry was retrospectively measured in 68 baseline biopsies available for biomarker analysis from 53 responders and 15 non-responders. No association between baseline CD20 expression and response was observed: CD20 was generally high and non-normally distributed (appendix p 15), and CD20 expression was similar in responders and non-responders (appendix p 15). Responses were observed in patients across a range that included low levels of CD20 expression (a minimum of 44% observed in responders; appendix p 15). Given the mode of action of mosunetuzumab, immune cell counts in peripheral blood were measured by flow cytometry at baseline to evaluate the potential effect on mosunetuzumab activity and during treatment to assess pharmacodynamic responses. At baseline, T-cell and natural killer (NK) cell counts were within the normal range, whereas B-cell counts were below the normal range in most patients, reflecting previous treatment (appendix p 15). No association between baseline B-cell, T-cell, or NK-cell counts and response was observed (appendix p 15). A rapid and sustained depletion of peripheral B cells was observed during treatment (appendix p 16). By contrast, T-cell and NK-cell counts were not significantly changed from baseline (appendix p 16).

The most common adverse events were cytokine release syndrome (in 40 [44%] of 90 patients), fatigue (in 33 [37%] patients), and headache (in 28 [31%] patients; table 3). The most common grade 3–4 adverse events were neutropenia or decreased neutrophil count (in 24 [27%] of 90 patients), hypophosphataemia (in 15 [17%] patients; all resolved with or without phosphate supplement), hyperglycaemia (in seven [8%] patients), and anaemia (in seven [8%] patients; table 3). 42 (47%) of 90 patients had a serious adverse event (appendix pp 8–9). One (1%) patient had a grade 5 (ie, fatal) adverse event of malignant neoplasm progression of follicular lymphoma and one (1%) died from an unknown cause (event occurred 31 days after the patient discontinued mosunetuzumab and without antecedent signs or symptoms); both events were considered unrelated to mosunetuzumab by the investigators. Four (4%) of 90 patients had adverse events leading to withdrawal from treatment; two events were considered related to mosunetuzumab (grade 2 cytokine release syndrome and grade 4 cytokine release syndrome, both resolved) and two were considered unrelated (grade 2 Hodgkin lymphoma [unresolved] and grade 4 Epstein-Barr viraemia [resolved]). Adverse event rates were similar in patients who were 65 years or younger, older than 65 years, and older than 70 years, and in patients with tumour burden above or below the median (appendix p 10).

Cytokine release syndrome was predominantly low grade; of all 90 patients, 23 (26%) patients had grade 1 and 15 (17%) had grade 2 cytokine release syndrome. Grade 3 cytokine release syndrome occurred in one (1%) patient and grade 4 cytokine release syndrome occurred in one (1%) patient with circulating lymphoma cells. Cytokine release syndrome primarily occurred during cycle 1 and was mostly associated with the step-up therapy on day 1 of cycle 1 (21 [23%] of 90) and target doses on day 15 of cycle 1 (32 [36%] of 88; appendix p 17). The one grade 3 cytokine release syndrome event

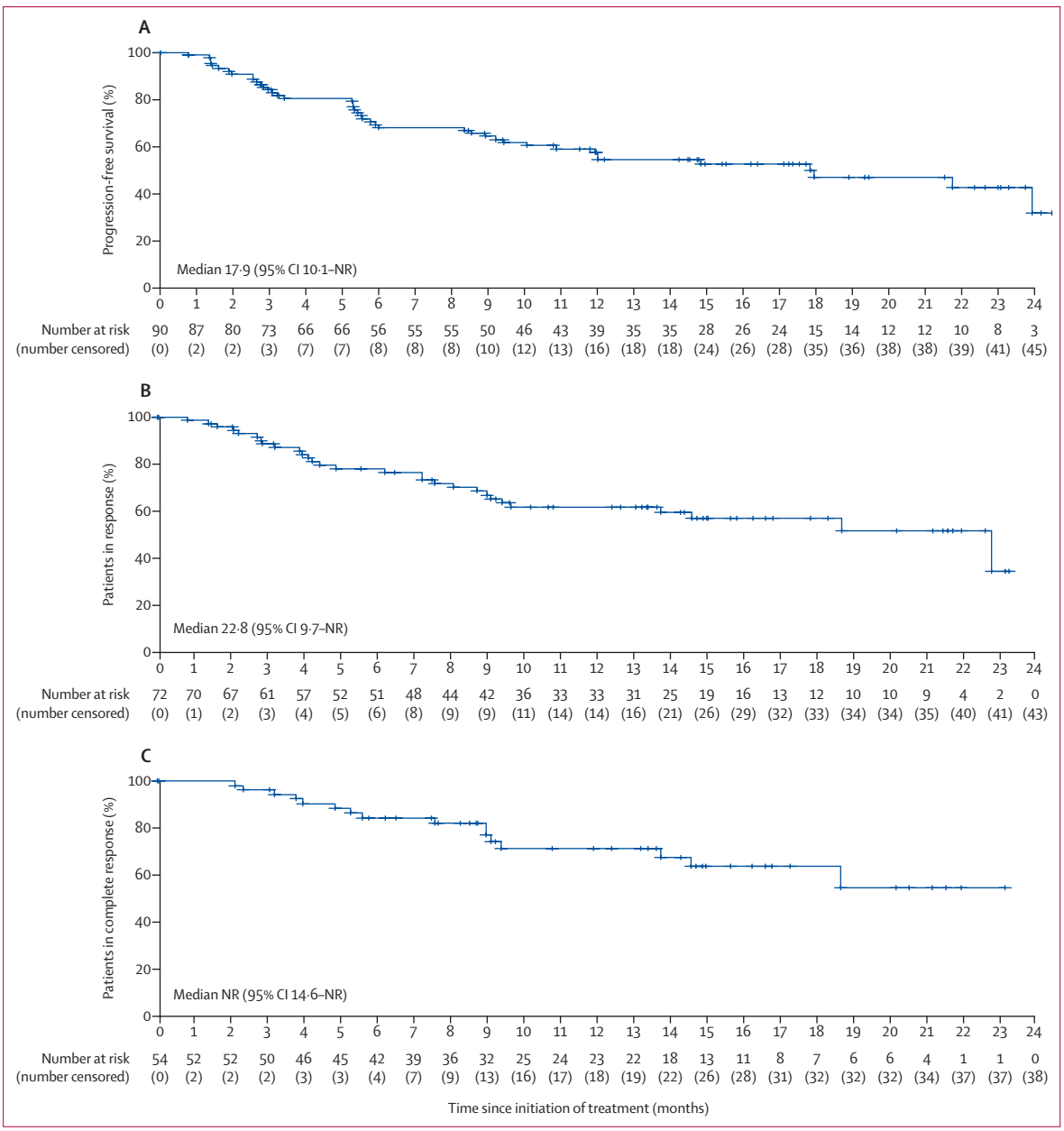

Figure 3: **Kaplan-Meier estimates of progression-free survival (A), duration of response (B), and duration of complete response (C) by independent review committee assessment**
NR=not reached.

occurred following target doses on day 1 of cycle 2, and one grade 4 cytokine release syndrome event occurred following target doses on day 15 of cycle 1. Cytokine release syndrome occurred more frequently in patients who were 65 years or younger (31 [50%] of 62) than in those older than 65 years (nine [32%] of 28). Median time to cytokine release syndrome onset was 5 h (IQR 3–9) after the start of mosunetuzumab infusion on day 1 of cycle 1, 20 h (9–31) after the start of mosunetuzumab infusion on day 8 of cycle 1, and 27 h (8–44) after the start of mosunetuzumab infusion on day 15 of cycle 1 (appendix p 17). Common cytokine release syndrome symptoms (ie, occurring in 20% or more of patients) were pyrexia (39 [98%] of 40 patients with cytokine release syndrome), hypotension (15 [38%]), chills (14 [35%]), headache (11 [28%]), tachycardia (11 [28%]), and hypoxia (eight [20%]). Among the 40 patients who developed cytokine release syndrome, six (15%) were managed with corticosteroids alone, three (8%) received tocilizumab alone, and four (10%) received both corticosteroids and tocilizumab (appendix p 11). For grade 2 cytokine release syndrome, seven (47%) of

	Grade 1–2	Grade 3	Grade 4
Cytokine release syndrome	38 (42%)	1 (1%)	1 (1%)
Fatigue	33 (37%)	0	0
Headache	27 (30%)	1 (1%)	0
Neutropenia or decreased neutrophil count	2 (2%)	12 (13%)	12 (13%)
Pyrexia	25 (28%)	1 (1%)	0
Hypophosphataemia	9 (10%)	15 (17%)	0
Pruritus	19 (21%)	0	0
Hypokalaemia	15 (17%)	2 (2%)	0
Cough	16 (18%)	0	0
Constipation	16 (18%)	0	0
Diarrhoea	15 (17%)	0	0
Nausea	15 (17%)	0	0
Rash	13 (14%)	1 (1%)	0
Dry skin	14 (16%)	0	0
Anaemia	5 (6%)	7 (8%)	0
Chills	11 (12%)	1 (1%)	0
Hypomagnesaemia	11 (12%)	0	0
Increased alanine aminotransferase	6 (7%)	4 (4%)	1 (1%)
Insomnia	11 (12%)	0	0
Arthralgia	10 (11%)	0	0
Peripheral oedema	10 (11%)	0	0
Abdominal pain	8 (9%)	1 (1%)	0
Back pain	8 (9%)	1 (1%)	0
Dizziness	9 (10%)	0	0
Urinary tract infection	8 (9%)	1 (1%)	0
Skin exfoliation	9 (10%)	0	0
Thrombocytopenia or decreased platelet count	5 (6%)	0	4 (4%)

Data are n (%). Data are for all exposed patients (n=90) and the most common adverse events occurring in 10% or more of patients with one or more adverse events. No treatment-related grade 5 adverse events occurred.

Table 3: **Treatment-emergent adverse events**

15 patients were admitted to hospital for monitoring and received fluids or oxygen, or both. For grade 1 cytokine release syndrome, 12 (52%) of 23 patients were hospitalised for monitoring and supportive management. Including the two patients with grade 3 and 4 cytokine release syndrome, a total of 21 (23%) of 90 patients were admitted to hospital for monitoring and treatment for cytokine release syndrome. The median duration of cytokine release syndrome was 3 days (IQR 2–4). All events of cytokine release syndrome resolved.

Common (ie, occurring in 10% or more of patients) haematological adverse events were neutropenia or decreased neutrophil count (in 26 [29%] of 90 patients), anaemia (12 [13%]), and thrombocytopenia or decreased platelet count (in nine [10%] patients; table 2). The median time to first neutropenia onset was 70 days (IQR 31–106) and median duration was 8 days (3–15). 18 (69%) of 26 patients received growth factor treatment; all patients had their neutropenia event resolved. No febrile neutropenia occurred.

Tumour flare occurred in three (3%) of 90 patients: one grade 2 pleural effusion (onset on day 43) and two grade 3 tumour flare (one with onset on day 11 and the other with onset on day 17). All events resolved (median duration 5 days [IQR 3–5·5]). Tumour lysis syndrome (grade 4) occurred in one patient (concurrent with grade 4 cytokine release syndrome in the patient with circulating lymphoma cells) and resolved after 5 days. Serious adverse events of infection occurred in 18 (20%) of 90 patients (13 [14%] patients had grade 3–4 serious infections); events that occurred in at least two patients were urinary tract infection (in three [3%] of 90 patients), pneumonia (two [2%]), COVID-19 (two [2%]), Epstein-Barr viraemia (two [2%]), and septic shock (two [2%]). Four (4%) of 90 patients had a confirmed or suspected COVID-19 infection, including two grade 1 and two grade 3 events. All confirmed or suspected COVID-19 infections resolved. Neurological adverse events observed by investigator assessment as related to mosunetuzumab and consistent with immune effector cell-associated neurotoxicity syndrome were confusional state (three [3%] of 90; grade 1–2), disturbance in attention (one [1%]; grade 1), and cognitive disorder (one [1%]; grade 1). All events resolved. No aphasia, seizures, encephalopathy, or cerebral oedema occurred.

Discussion

In this study, fixed-duration mosunetuzumab induced a high proportion of objective responses and complete responses in a heavily pretreated population of patients with relapsed or refractory follicular lymphoma. The study met its primary efficacy endpoint, with a complete response rate of 60·0%. Response rates were generally consistent across patient subgroups with risk factors for poor prognosis, although the small patient numbers in some of these subgroups should be noted. Responses occurred early in the treatment course and were durable.

Potential biomarkers associated with mosunetuzumab's mechanism of action were assessed for correlation with response. CD20 was generally high and non-normally distributed, making the assessment with response challenging; however, responses were seen across all observed CD20 levels. Additionally, quantitative measurements of lymphocyte populations in peripheral blood showed the effects of previous treatments on the immune profile in the relapsed or refractory setting. Although B-cell counts were lower than the normal range in most patients because of previous treatments, there was a range of T-cell levels, and responses were observed across these levels.

For patients with relapsed or refractory follicular lymphoma who have received two or more previous lines of therapy, the currently approved treatment options have distinct safety and efficacy profiles. In the current study, the complete response rate was significantly higher than the 14% historical control complete response rate with the PI3K inhibitor copanlisib, which was observed in a similar population of patients with relapsed

or refractory follicular lymphoma and two or more previous lines of therapy (n=104) in a phase 2 trial.[12,14] In the pivotal studies evaluating PI3K inhibitors in patients with relapsed or refractory follicular lymphoma and two or more previous therapies as a whole, objective response rates ranged between 42% and 59%, but complete remissions were infrequent (1–14%).[12,14–20] A similar pattern of response was observed in the pivotal study evaluating the EZH2 inhibitor tazemetostat in patients with relapsed or refractory follicular lymphoma and two or more previous lines of therapy whose tumours had *EZH2* mutations (objective response rate 69% and complete response rate 12%), whereas response rates in patients with wild-type *EZH2* were lower (objective response rate 34% and complete response rate 4%).[21,22] In addition to the higher response rates, mosunetuzumab also showed improved efficacy across secondary endpoints in our trial, with longer durable responses and longer progression-free survival estimates than observed for PI3K inhibitors and tazemetostat. For example, the median duration of response was 12·2 months with copanlisib[12] and 10·9 months with tazemetostat[21] (in patients with a *EZH2* mutation), versus 22·8 months with mosunetuzumab.

Response rates in the current study are more similar to those observed in studies evaluating chimeric antigen receptor (CAR) T-cell therapies in patients with relapsed or refractory follicular lymphoma and two or more previous lines of therapy, in which high objective response rates (86–94%) and complete response rates (60–79%) were reported, along with durable remissions at relatively short follow-up.[23–25] With a median follow-up of 18·3 months, responses in the current study of mosunetuzumab were also durable, and were maintained for 18 months or longer in 70·2% of complete responders and 56·9% of all responders. Both CAR T-cell therapies and bispecific antibodies are likely to have essential roles in the future management of relapsed or refractory follicular lymphoma. Of note, however, mosunetuzumab is an off-the-shelf immunotherapy that avoids many of the logistical challenges associated with current CAR T-cell therapies, including the need for leukapheresis, lymphodepleting chemotherapy, and centralised manufacturing with an extended lead time (median 17–29 days[25–27]); complicated insurance approvals and restricted access to authorised treatment centres might also delay or limit treatment with CAR T-cell therapies, and subject patients to additional anti-lymphoma therapy for bridging.

In the current study, mosunetuzumab had a manageable safety profile that was consistent with the phase 1 results[8] and was similar in older and younger patients. Notably, adverse events leading to mosunetuzumab discontinuation were rare and occurred in only four patients. In the pivotal studies of the PI3K inhibitors, adverse events leading to discontinuation occurred in 15–35% of patients.[12,15,17,19]

Cytokine release syndrome is a potentially serious complication of T-cell-engaging immunotherapy. In the phase 1 study, cycle 1 step-up dosing provided effective cytokine release syndrome mitigation.[8] In the phase 2 study, cytokine release syndrome was predominantly grade 1–2 and primarily confined to cycle 1. Most patients with cytokine release syndrome were managed without steroids or tocilizumab. All cytokine release syndrome events resolved. In the ZUMA-5 trial of axicabtagene ciloleucel in patients with relapsed or refractory follicular lymphoma and two or more previous therapies, cytokine release syndrome (as per the Lee criteria[28]) occurred in 97 (78%) of 124 patients (grade ≥3 cytokine release syndrome in 6%), with one grade 5 multisystem organ failure in the setting of cytokine release syndrome.[23] In the ELARA trial of tisagenlecleucel in patients with relapsed or refractory follicular lymphoma and two or more previous therapies, cytokine release syndrome (as per the Lee criteria[28]) occurred in 47 (48%) of 97 patients, with 6% of patients requiring vasopressors.[25]

Neutropenia was the most common haematological adverse event, with no febrile neutropenia and manageable with growth factor support. No grade 5 (ie, fatal) adverse events due to infection were reported. Hypophosphataemia was a commonly reported biochemical adverse event but was not associated with clinically significant sequelae. Grade 3–4 hypophosphataemia has also been observed with CAR T-cell therapies in patients with non-Hodgkin lymphoma.[24] The cause of hypophosphataemia is not entirely understood, but a role of interleukin-6 has been hypothesised.[29]

Neurological adverse events assessed by the investigator as related to mosunetuzumab and consistent with immune effector cell-associated neurotoxicity syndrome were rare, with confusional state (grade 1–2 only) observed in three (3%) of 90 patients, and no aphasia, seizures, encephalopathy, or cerebral oedema. In ZUMA-5, confusional state occurred in 35 (24%) of 148 patients (5% were grade 3).[23] In ELARA, immune effector cell-associated neurotoxicity syndrome occurred in four (4%) of 97 patients, with one grade 4 event reported.[25] Notably, the seemingly increased potential for high-grade neurological toxicity, along with cytokine release syndrome and the requirement for chemotherapy-based lymphodepletion before administration, might limit the use of CAR T-cell therapies in some vulnerable populations, such as older or less fit patients. The favourable safety profile of mosunetuzumab allows administration as an outpatient regimen, which might be particularly impactful in the current era with limited availability of hospital beds, and also enables patient access in community-based practices.

To our knowledge, the current study of mosunetuzumab in patients with relapsed or refractory follicular lymphoma and two or more previous therapies is the first to report the efficacy and safety of a CD20×CD3 bispecific antibody at the recommended dose and in a

pivotal phase 2 setting. Several other CD20×CD3 bispecific antibodies are in development for non-Hodgkin lymphoma, with promising anti-lymphoma activity observed in dose-escalation studies involving patients with relapsed or refractory non-Hodgkin lymphoma, including those with relapsed or refractory follicular lymphoma. Notably, in ten patients with relapsed or refractory follicular lymphoma who received epcoritamab subcutaneously at doses of at least 0·76 mg, an objective response rate of 90% and a complete response rate of 50% were observed.[30] Moreover, in 44 patients with relapsed or refractory follicular lymphoma who received glofitamab intravenously at target doses of 10 mg or more, the objective response rate was 69·0% and complete response rate was 58·6%.[31] However, head-to-head studies are currently not available and cross-study comparisons are limited by differences in sample size, patient population, and study design. Some agents also require patients to be admitted to hospital for treatment initiation or are given as treat-to-progression regimens, or both.

The effect of the COVID-19 pandemic on the study was minor, with a low frequency of COVID-19 infections. The interpretation of this study, however, is limited by the single-arm design, although a robust historical control[12] was identified to inform the analysis of the primary endpoint. Previous exposure to immunomodulatory agents was low, although activity was observed in patients with previous rituximab plus lenalidomide. The median follow-up was relatively short for a study about follicular lymphoma, and additional follow-up is planned.

With a median follow-up of 18·3 months, fixed-duration mosunetuzumab demonstrated high complete response rates and durable remissions in patients with relapsed or refractory follicular lymphoma and two or more previous therapies, including those with high-risk disease. Mosunetuzumab has a favourable safety profile, with cycle 1 step-up dosing providing effective cytokine release syndrome mitigation, allowing administration as an outpatient regimen.

Contributors

LEB, LHS, MCW, SY, C-CL, HH, AK, and NLB did the conception and study design. All authors did the data acquisition. LEB, NLB, MCW, SY, C-CL, HH, AK, and EP had access to and verified all raw data. EP, MCW, SY, C-CL, HH, and AK did the data analysis. All authors contributed to the data interpretation, drafting or critical revision of the Article, and are accountable for all aspects of the work. All authors had access to all of the data.

Declaration of interests

LEB reports consulting fees from Genentech, ADC Therapeutics, Merck, AstraZeneca, and Amgen; and participation on a data safety monitoring board for Ziopharm Oncology. LHS reports research grants from Roche/Genentech and Teva; consulting fees from AbbVie, Acerta, Amgen, AstraZeneca, Celgene/Bristol-Myers Squibb (BMS), Gilead/Kite/Incyte, Janssen, Roche/Genentech, MorphoSys, Sandoz, and TG therapeutics; and honoraria from AbbVie, Acerta, Amgen, AstraZeneca, Celgene/BMS, Gilead/Kite/Incyte, Janssen, Roche/Genentech, MorphoSys, Sandoz, and TG therapeutics. MM reports research grants from AstraZeneca, Genentech, Janssen, Roche, Bayer, IGM Biosciences, Pharmacyclics, and Seattle Genetics; payment or honoraria from lectures, presentations, speaker's bureaus or manuscript writing, or educational events from ADC Therapeutics, Bayer, Daiichi Sankyo, MEI Pharma, Genentech, Seattle Genetics, Epizyme, IMV Therapeutics, Janssen, Pharmacyclics, and Roche; payment from expert testimony from Bayer; and owns stock or stock options in Merck. SJS reports grants or contracts from Genentech, AbbVie, Acerta, AstraZeneca, Celgene/BMS/Juno, Incyte, Merck, Novartis, TG Therapeutics, and Theredex; consulting fees from AstraZeneca, BeiGene, Celgene/BMS/Juno, Genentech/Roche, Genmab, Incyte, Janssen, MorphoSys, Mustang Biotech, Novartis, and Regeneron; payment or honoraria from lectures, presentations, speaker's bureaus or manuscript writing, or educational events for Incyte, Novartis, and Takeda; participation on a monitoring board or advisory board for AstraZeneca, BeiGene, Celgene/BMS/Juno, Genentech/Roche, Genmab, Incyte, Janssen, MorphoSys, Mustang Biotech, Novartis, and Regeneron; a role in board, society, committee, or advocacy groups for Genentech, Legend Biotech, Novartis, and Nordic Nanovector; and research support for Genentech and Merck. SA reports research grants from AbbVie, Roche, Genentech, Takeda, Lilly, and Merck; speaker's bureau from Pfizer; and is chair of the haematology group (unpaid) of the Canadian Cancer Trials Group. JK reports research grants from Roche, AstraZeneca, and Merck; consulting fees from AbbVie, Antengene, BMS, Gilead, Karyopharm, Medison Ventures, Merck, Roche, and Seattle Genetics; payment or honoraria from lectures, presentations, and educational events for AbbVie, Amgen, AstraZeneca, BMS, Gilead, Incyte, Janssen, Karyopharm, Merck, Novartis, Pfizer, Roche, and Seattle Genetics; participation in a data safety monitoring board for Karyopharm; and participation as chair, scientific advisory board, and director in the board of directors for Lymphoma Canada. MC reports consulting fees from BeiGene, BMS, Incyte, Janssen, Kite, Kyowa, Miltenyi Biotec, Novartis, Roche, and Takeda; payment from lectures, presentations, speaker's bureaus or manuscript writing, or educational events from Amgen, Eusa Pharma, Janssen, Kite, Kyowa, Roche, and Takeda; and meeting attendance or travel support, or both, from Kite, Janssen, Roche, Sanofi, and Takeda. LN reports grants from BMS, Caribou Biosciences, Epizyme, Gilead/Kite, Janssen, IGM Biosciences, Takeda, and TG Therapeutics; payment or honoraria from lectures, presentations, speaker's bureaus or manuscript writing, or educational events from Genentech, Gilead/Kite, and Takeda; meeting attendance or travel, or both, support from Genentech; and participation in data safety monitoring board or advisory board for ADC Therapeutics, Bayer, Epizyme, BMS, MorphoSys, Novartis, Genentech, Takeda, MEI, DeNovo, and TG Therapeutics. CYC reports payment or honoraria from lectures, presentations, speaker's bureaus or manuscript writing, or educational events for Janssen, AstraZeneca, Roche, and Beigene; and participation in data safety monitoring board or advisory board for Roche, Janssen, TG Therapeutics, AstraZeneca, Lilly, and Gilead. MCW reports meeting attendance or travel support, or both, from Roche/Genentech; and stocks and stock options in Roche. SY reports meeting attendance or travel support, or both, for Genentech; patents planned, issued, or pending from Genentech; and stocks and stock options in Genentech. C-CL reports stocks and stock options in Roche; and patents planned, issued, or pending for Genentech. AK reports stocks or stock options in Roche. EP reports stocks or stock options in Genentech. NLB reports research funding from ADC Therapeutics, Affimed, Autolus, BMS, Celgene, Forty Seven, Immune Design, Janssen, Kite Pharma, Merck, Millennium, Pfizer, Pharmacyclics, Roche/Genentech, and Seattle Genetics. All other authors declare no competing interests.

Data sharing

The study protocol and statistical analysis plan are available in the appendix. For eligible studies, qualified researchers might request access to individual patient level clinical data through a data request platform. At the time of writing, the request platform is Vivli. Up-to-date details about Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents can be found online. Anonymised records for individual patients across more than one data source external to Roche cannot, and should not, be linked because of a potential increase in risk of patient re-identification.

For the **data request platform** see https://vivli.org/ourmember/roche/

For more on **Roche's Global Policy on the Sharing of Clinical Information** see https://go.roche.com/data_sharing

Acknowledgments

This study was funded by F Hoffmann-La Roche and Genentech. We thank the patients and their families, as well as the study investigators, coordinators, nurses, and representatives of the funder, in particular Michelle Doral and Iris To, who were involved in data collection and analysis. Third party medical writing assistance, under the direction of LEB and SY, was provided by Scott Malkin and Helen Cathro of Ashfield MedComms, an Ashfield Health company, and was funded by F Hoffmann-La Roche.

References

1 Dreyling M, Ghielmini S, Rule G, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2021; **32:** 298–308.

2 Bachy E, Seymour JF, Feugier P, et al. Sustained progression-free survival benefit of rituximab maintenance in patients with follicular lymphoma: long-term results of the PRIMA study. *J Clin Oncol* 2019; **37:** 2815–24.

3 Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. *N Engl J Med* 2017; **377:** 1331–44.

4 Rivas-Delgado A, Magnano L, Moreno-Velázquez M, et al. Response duration and survival shorten after each relapse in patients with follicular lymphoma treated in the rituximab era. *Br J Haematol* 2019; **184:** 753–59.

5 Bachy E, Cerhan JR, Salles G. Early progression of disease in follicular lymphoma is a robust correlate but not a surrogate for overall survival. *Blood Adv* 2021; **5:** 1729–32.

6 Seymour JF, Marcus R, Davies A, et al. Association of early disease progression and very poor survival in the GALLIUM study in follicular lymphoma: benefit of obinutuzumab in reducing the rate of early progression. *Haematologica* 2019; **104:** 1202–08.

7 Sun LL, Ellerman D, Mathieu M, et al. Anti-CD20/CD3 T cell-dependent bispecific antibody for the treatment of B cell malignancies. *Sci Transl Med* 2015; **7:** 287ra70.

8 Budde LE, Assouline S, Sehn LH, et al. Single-agent mosunetuzumab shows durable complete responses in patients with relapsed or refractory B-cell lymphomas: phase I dose-escalation study. *J Clin Oncol* 2022; **40:** 481–91.

9 Assouline SE, Kim WS, Sehn LH, et al. Mosunetuzumab shows promising efficacy in patients with multiply relapsed follicular lymphoma: updated clinical experience from a phase I dose-escalation trial. *Blood* 2020; **136:** 42–44.

10 Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; **25:** 579–86.

11 Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant* 2019; **25:** 625–38.

12 Dreyling MH, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. *J Clin Oncol* 2017; **35:** 3898–905.

13 Casulo C, Larson MC, Lunde JL, et al. Treatment patterns and outcomes of patients with relapsed or refractory follicular lymphoma receiving three or more lines of systemic therapy (LEO CReWE): a multicentre cohort study. *Lancet Haematol* 2022; **9:** e289–300.

14 US Food and Drug Administration. ALIQOPA: prescribing information, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209936s004lbl.pdf (accessed Jan 26, 2022).

15 Flinn IW, Miller CB, Ardeshna KM, et al. DYNAMO: a phase II study of duvelisib (IPI-145) in patients with refractory indolent non-Hodgkin lymphoma. *J Clin Oncol* 2019; **37:** 912–22.

16 US Food and Drug Administration. COPIKTRA: prescribing information, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211155s000lbl.pdf (accessed Jan 26, 2022).

17 Fowler NH, Samaniego F, Jurczak W, et al. Umbralisib, a dual PI3Kδ/CK1ε inhibitor in patients with relapsed or refractory indolent lymphoma. *J Clin Oncol* 2021; **39:** 1609–18.

18 US Food and Drug Administration. UKONIQ: prescribing information. 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213176s000lbl.pdf (accessed Jan 26, 2022).

19 Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med* 2014; **370**: 1008–18.

20 US Food and Drug Administration. ZYDELIG: prescribing information. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205858s014lbl.pdf (accessed Jan 26, 2022).

21 Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. *Lancet Oncol* 2020; **21:** 1433–42.

22 US Food and Drug Administration. TAZVERIK: prescribing information. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213400s000lbl.pdf (accessed Jan 26, 2022).

23 Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. *Lancet Oncol* 2021; **23:** 91–103.

24 US Food and Drug Administration. YESCARTA (axicabtagene ciloleucel). 2021. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel (accessed Jan 26, 2022).

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

26 Tyagarajan S, Spencer T, Smith J. Optimizing CAR-T cell manufacturing processes during pivotal clinical trials. *Mol Ther Methods Clin Dev* 2019; **16:** 136–44.

27 van de Wiel L, Hallard D, Ensari S, et al. Manufacturing commercial axicabtagene ciloleucel for European patients: a 2-year retrospective analysis. *HemaSphere* 2021; **5:** 691.

28 Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014; **124:** 188–95.

29 Uppal NN, Workeneh BT, Rondon-Berrios H, Jhaveri KD. Electrolyte and acid-base disorders associated with cancer immunotherapy. *Clin J Am Soc Nephrol* 2022; **7:** 922–33.

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

31 Hutchings M, Morschhauser F, Iacoboni G, et al. Glofitamab, a novel, bivalent CD20-targeting T-cell-engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a phase I trial. *J Clin Oncol* 2021; **39:** 1959–70.