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Odronextamab, a human CD20×CD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial

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RB, AC, SRA, JL, IL, and MST conceptualised the study. SRA, MU, and AC did the study design and amendments. RB, JEA, RHA, JRB, JNA, SMA, JAB, SMO, JCC, JD, AR, JLC, and MST recruited patients and collected the data. AC, SRA, MU, MZ, and JL contributed to data curation and data analysis. None of the authors received payment related directly to the development of this publication. All authors had full access and verified the data and contributed to data interpretation. RB and MST have accessed and verified all the data in the study. All authors provided critical review, revision, and approval of the manuscript, and the decision to submit for publication.

Declaration of interests

RB reports research funding from Regeneron Pharmaceuticals, paid to his institution; institutional payments for sponsored studies from AbbVie, Genentech, Pharmacyclics, and Roche; non-financial participation on advisory boards for Janssen Biotech; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from the 18th Annual International Ultmann Chicago Lymphoma Symposium and Curio Science–opinions in diffuse large B cell lymphoma; and his spouse holds stock options and is an employee of Sanofi-Pasteur. JEA reports participation on a data safety monitoring board or advisory board for Bristol Myers Squibb, Juno, and Regeneron Pharmaceuticals. RHA reports advisory board membership from ADC Therapeutics, Bristol Myers Squibb, Epizyme, Genentech, Gilead, Incyte, Karyopharm, Portola, and Seattle Genetics; and institutional research funding from Cyteir, Forty Seven, Genentech, Gilead, Janssen, Regeneron Pharmaceuticals, and Roche. JRB reports sponsored research funding paid to her institution from Gilead, Lilly (Loxo), SecuraBio (Verastem), Sun, and TG Therapeutics; consulting fees from AbbVie, Acerta, AstraZeneca, BeiGene, Bristol Myers Squibb, Catapult Therapeutics, Celgene, Dynamo Therapeutics, Eli Lilly and Company, Gilead, Genentech, Hutchmed, Janssen, Juno, Kite, Loxo, MEI Pharma, Morphosys, Nextcea, Novartis, Octapharma, Pfizer, Pharmacyclics, Rigel, Roche, Sunesis, TG Therapeutics, and Verastem; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Janssen; and participation on a data safety monitoring board or advisory board for Invectys and Morphosys. JNA reports grants or contracts from Celgene, Genentech, Janssen, and TG Therapeutics, paid to his institution; consulting fees from AbbVie, ADC Therapeutics, Ascentage, AstraZeneca, BeiGene, Epizyme, Genentech, Janssen, Pharmacyclics, and TG Therapeutics; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AbbVie, AstraZeneca, BeiGene, Janssen, and PCYC; payment for expert testimony from Calderhead and Lockemeyer Peschke; support for attending meetings and travel from AstraZeneca, BeiGene, and Janssen; and non-financial participation on a data safety monitoring board or advisory board for AstraZeneca. SMO reports consulting fees from AbbVie, Alexion, Amgen, Aptose Biosciences, Astellas, Autolus, Bristol Myers Squibb, Celgene, Eli Lilly and Company, GlaxoSmithKline, Janssen Oncology, Johnson and Johnson, Juno Therapeutics, Merck, NOVA Research, Vaniam, Verastem, and Vida Ventures; research support from Acerta, Caribou, Kite, and Regeneron Pharmaceuticals; and consultant and research support from Gilead, Pfizer, Pharmacyclics, Sunesis, and TG Therapeutics. JCC reports consulting fees from AbbVie, ADC Therapeutics, Janssen, Kymera, Novartis, and TenBio; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, BeiGene, Bristol Myers Squibb, Epizyme, and Morphosys. JLC reports research funding from AbbVie, Bayer, Merck, and Roche; and participation on a data safety monitoring board or advisory board for Incyte and Karyopharm. IL reports patents from Regeneron Pharmaceuticals for tumour treatment methods using CD20xCD3 bispecific antibody (US10662244) and a dosing strategy that mitigates cytokine release syndrome for therapeutic antibodies (US20200129617); and holds stock or stock options and is an employee of Regeneron Pharmaceuticals. MST reports research funding from Regeneron Pharmaceuticals; consulting fees from Gilead, Janssen, Kite, Novartis, Regeneron Pharmaceuticals, and Roche; and support for attending meetings or travel from Amgen and Janssen, or both. MU, JL, MZ, SRA, and AC hold stock or stock options for and are employees of Regeneron Pharmaceuticals. All other authors declare no competing interests.

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Summary

Background—Odronextamab is a hinge-stabilised, fully human IgG4-based CD20×CD3 bispecific antibody that binds CD3 on T cells and CD20 on B cells. We aimed to evaluate the safety and antitumour activity of odronextamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma.

Methods—This single-arm, multicentre, phase 1, dose-escalation and dose-expansion (ELM-1) trial was conducted at ten academic sites across the USA and Germany. Patients aged 18 years or older with CD20-positive relapsed or refractory B-cell malignancies who previously received CD20-directed antibody therapy and who had at least one measurable lesion, and an ECOG performance status of 0 or 1 were included. Patients received intravenous odronextamab, according to a step-up dosing schedule in cycle 1, followed by treatment once per week at target doses ranging from 0·1 mg to 320 mg during cycles 2–4 (each cycle was 21 days). After cycle 4, maintenance treatment occurred every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint of safety was assessed by the incidence of adverse events and dose-limiting toxicities to determine the maximum tolerated dose or phase 2 dose of odronextamab, or both. Preliminary antitumour activity, as measured by objective response rate, was a secondary endpoint. This study is registered with ClinicalTrials.gov, NCT02290951.

Findings—From Feb 4, 2015, to Sept 25, 2021, 145 heavily pretreated patients (median of 3 (IQR 2–5] previous therapies) were enrolled (94 to the dose-escalation and 51 to the dose-expansion part of the study). The median age of patients was 67·0 years (IQR 57·0–73·0); 101 (70%) were male and 44 (30%) were female; most participants were White (119 [82%]) and not Hispanic or Latino (132 [91%]). 42 (29%) patients received previous CAR T therapy and 119 (82%) were refractory to the last line of therapy. Median duration of follow-up was 4·2 months (IQR 1·5–11·5). During dose escalation, odronextamab was administered up to the maximum dose of 320 mg once per week and no dose-limiting toxicities were observed. The recommended dose for expansion in patients with follicular lymphoma grade 1–3a was 80 mg and was 160 mg for patients with diffuse large B-cell lymphoma. Cytokine release syndrome and neurological treatment-emergent adverse events were predominantly low grade and did not result in treatment discontinuation. The most common grade 3 or worse treatment-emergent adverse events were anaemia (36 [25%]), lymphopenia (28 [19%]), hypophosphataemia (27 [19%]), neutropenia (27 [19%]), and thrombocytopenia (20 [14%]). Serious treatment-emergent adverse events occurred in 89 (61%) of 145 patients; the most frequent were cytokine release syndrome (41 [28%]), pyrexia (11 [8%]), pneumonia (nine [6%]), and infusion-related reaction (six [4%]). Four deaths were considered related to treatment (gastric perforation in a patient with gastric involvement by lymphoma, lung infection, pneumonia, and tumour-lysis syndrome). Objective response rate was 51% (95% CI 42–59; 72 of 142). In patients with follicular lymphoma who received odronextamab doses of 5 mg or higher, the objective response rate was 91% (95% CI 75–98; 29 of 32) and the complete response rate was 72% (95% CI 53–86; 23 of 32). In patients with diffuse large B-cell lymphoma without previous CAR T-cell therapy who received doses of 80 mg or higher, the objective response rate was 53% (eight of 15) and all responses were complete responses. In patients with diffuse large B-cell lymphoma who had previous CAR T-cell therapy and received doses of 80 mg or higher, the objective response rate was 33% (ten of 30) and complete response rate was 27% (eight of 30).

Interpretation—Odronextamab monotherapy showed a manageable safety profile and encouraging preliminary activity, including durable responses in heavily pretreated patients with B-cell non-Hodgkin lymphoma, supporting further clinical investigation in phase 2 and 3 trials.

Funding—Regeneron Pharmaceuticals.

Introduction

Bispecific antibodies have emerged as a promising anticancer method and are being investigated for the treatment of patients with relapsed or refractory B-cell non-Hodgkin lymphoma.[1–5] Bispecific antibodies used in cancer treatment possess two antigen-binding fragment arms; one arm targets a tumour-expressing antigen and the second binds to a T-cell activating receptor, inducing potent eradication of tumour cells.[1,4,5]

Odronextamab (REGN1979) is a hinge-stabilised CD20×CD3 bispecific antibody that binds to CD3 on T cells and CD20 on B cells, triggering T-cell-mediated cytotoxicity independent of T-cell receptor recognition.[6] It is fully human, IgG4-based, and heterodimeric with a common light chain purified by selective protein A chromatography. Preclinical evaluation has shown that this investigational drug can induce activation of T cells and lysis of CD20-expressing B cells in vitro, and has antitumour activity in mouse tumour models.[6] In cynomolgus monkeys, odronextamab potently and durably depleted B cells in the circulation, lymph nodes, and spleen.[6]

Here we report findings from the first-in-human study investigating the safety and antitumour activity of odronextamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma.

Methods

Study design and participants

This single-arm, multicentre, phase 1, dose-escalation and dose-expansion (ELM-1) trial was conducted at ten academic sites across the USA and Germany (appendix p 9). Patients aged 18 years or older with CD20-positive B-cell malignancies who previously received CD20-directed antibody therapy were included. A 3 + 3 design[7,8] was used for dose escalation (appendix p 8). At data cutoff (Sept 25, 2021), the expansion cohort of patients with diffuse large B-cell lymphoma who received chimeric antigen receptor (CAR) T-cell therapy was still being enrolled. Data from a cohort of patients with chronic lymphocytic leukaemia will be analysed separately.

Patients were eligible for enrolment if they had documented B-cell non-Hodgkin lymphoma (as defined by 2007 NCI working group criteria), at least one measurable lesion of at least 1·5 cm on the longest diameter, at least one previous treatment with an anti-CD20 antibody, ECOG performance status of 0 or 1, and adequate haematological and organ function (platelet count ≥75×10^9 cells per L, haemoglobin ≥9·0 g/dL, absolute neutrophil count ≥1·0 ×10^9 cells per L, aspartate aminotransferase and alanine aminotransferase ≤2·5 times the upper limit of normal, total bilirubin ≤1·5 times the upper limit of normal, and creatinine clearance ≥50 mL/min). Patients with bone marrow involvement or splenic sequestration

were included if they met the haematologic parameters (platelet count ≥25×10^9 cells per L, haemoglobin ≥7·0 g/dL, and absolute neutrophil count ≥0·5 ×10^9 per L). Patients with primary CNS lymphoma or previous allogeneic haematopoietic stem-cell transplantation were excluded. Full details of the inclusion and exclusion criteria are provided in the appendix (pp 2–3).

All participants provided written informed consent. The research protocol was designed by Regeneron Pharmaceuticals and approved by relevant institutional review boards and ethics committees at each site (appendix p 9). The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki.

Procedures

Eligible patients received intravenous odronextamab (Regeneron Pharmaceuticals, Tarrytown, NY, USA), according to a step-up dosing schedule in cycle 1, followed by treatment once per week at target doses ranging from 0·1 mg to 320 mg during cycles 2–4 on days 1, 8, and 15 (each cycle was 21 days; appendix pp 8, 15). After cycle 4, maintenance treatment occurred every 2 weeks until disease progression or unacceptable toxicity. Prophylactic measures to mitigate the risk of cytokine release syndrome, including steroid prophylaxis, split dosing, and step-up dosing were implemented during dose escalation and were further optimised with dose expansion, as well as in an ongoing phase 2 study of odronextamab monotherapy in patients with relapsed or refractory B-cell non-Hodgkin lymphoma (NCT03888105).

On-site availability of tocilizumab had to be confirmed before step-up dosing. Odronextamab was administered intravenously over 4 h during cycle 1 (days 1, 2, 8, 9, 15, and 16), with the first full dose administered on day 1 of cycle 2. The infusion duration was decreased to 60 min for subsequent doses during cycles 2–4 and during maintenance treatment. Patients were monitored in an inpatient setting for approximately 24 h after the end of each infusion during cycle 1 and day 1 of cycle 2. Subsequent doses were administered in the outpatient setting. Premedication was administered to further mitigate the risk of cytokine release syndrome during cycle 1 (appendix p 4, 15). Briefly, prophylactic steroids were given 1 day before, on the day of, and 1 day after the infusion. Additionally, paracetamol and diphenhydramine were given 30–60 min before the infusion. Steroid premedication was tapered for the day 8 dose in cycle 2 and all premedication was discontinued for subsequent doses. Key clinical and laboratory assessments during the screening or at baseline and treatment periods are provided in the appendix (p 10).

Dose reductions, interruptions, or discontinuations were permitted to manage adverse events. The severity of adverse events was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03),[9] and cytokine release syndrome was graded according to modified Lee and colleagues 2014 or 2019 criteria,[10,11] depending on the patient enrolment date. Adverse events were deemed related to the study drug per investigator assessment. Per protocol, a serious adverse event was defined as any untoward medical occurrence which results in death, is life-threatening, requires hospital admission or longer existing stay in hospital, results in persistent or significant disability, congenital

anomaly, or is considered an important medical event that might jeopardise the patient or require intervention to prevent other serious outcomes. Patients with grade 3 or worse toxic effects were required to hold study treatment temporarily until the toxic effects improved to grade 1 or baseline level. Patients who had grade 3 cytokine release syndrome or tumour lysis syndrome after the intermediate or full dose had a 50% dose reduction for the subsequent dose, which was then escalated to the full dose as tolerated. Grade 4 cytokine release syndrome required permanent discontinuation of the study drug. As part of an earlier amendment (Dec 15, 2015), retreatment at higher doses was permitted during dose escalation for patients who showed a clinical benefit and then relapsed. The protocol was subsequently amended (Dec 17, 2019) to remove retreatment when the maintenance dosing period was extended to progression. Criteria for a patient to be removed from the study are provided in the appendix (p 4).

The treatment-emergent period was defined as time from first administration of the study drug to 90 days after the last dose. Relative dose intensity was defined as actual dose intensity (ie, the administered dose per unit of time) divided by the planned dose intensity. Consensus criteria for immune effector cell-associated neurotoxicity syndrome-like events were unavailable before the initiation of this study; therefore, a sponsor-defined list of approximately 140 terms in the nervous system disorders and psychiatric disorders system organ classes from the Medical Dictionary for Regulatory Activities was used (version 23.1; appendix p 6). Defining criteria included the occurrence of dose-limiting toxicities during the first 28 days of treatment and consideration by the investigator as being at least possibly related to the treatment (appendix p 4).

Objective response rate was assessed every 12 weeks according to the revised response criteria for malignant lymphoma by the National Cancer Institute International Working Group,[12] using the Lugano classification.[13] Details of radiographic assessments are provided in the appendix (p 7). Blood samples to measure odronextamab concentration were collected with dense pharmacokinetic sampling during weeks 1–12 (cycles 1–4) and less dense sampling was done thereafter. Odronextamab concentrations in serum were measured using a validated enzyme-linked immunosorbent assay (Regeneron Pharmaceuticals, Tarrytown, NY, USA) with lower limit of quantification of 0·003 mg/L.

Patients were permitted to receive supportive care medications as needed for the management of cytokine release syndrome (including antipyretics, corticosteroids, intravenous fluids, vasopressors, tocilizumab, oxygen, and mechanical ventilation), hypouricaemic agents for management of tumour lysis syndrome, and anti-infective prophylaxis as per local institutional guidelines (including *Pneumocystis jirovecii* pneumonia prophylaxis, intravenous immunoglobulin supplementation, and appropriate antiviral prophylaxis for patients with previous herpes simplex virus, cytomegalovirus, or hepatitis B virus infections). Transfusion of blood products and granulocyte colony-stimulating factor use were permitted as per standard of care.

Outcomes

The primary endpoint of safety was assessed by the incidence of adverse events and dose-limiting toxicities to determine the maximum tolerated dose or phase 2 dose of

odronextamab, or both. Key secondary endpoints were pharmacokinetics; immunogenicity; anti tumour activity as measured by objective response rate (ie, proportion of patients with the best overall complete or partial response per Lugano classification), duration of response (ie, time from first complete or partial response to disease progression or death), and progression-free survival (ie, time from start of treatment to disease progression or death); and overall survival. The duration of follow-up was extended from 6 to 15 months and subsequently, further extended to the duration of the study (appendix p 5), and patients were not consistently followed-up for survival; consequently, survival data are not reported. Overall survival will be reported for patients in the expansion cohort at a later date when the cohort survival data are mature.

Statistical analysis

There were no formal statistical hypotheses in this study. A sample size of 102 patients with B-cell non-Hodgkin lymphoma was determined for dose escalation on the basis of 3 + 3 design and number of dose levels. A total of 130 patients with B-cell non-Hodgkin lymphoma were planned for inclusion in expansion cohorts to further evaluate the safety and activity of recommended doses. At the clinical cutoff date (Sept 25, 2021), enrolment was ongoing in the diffuse large B-cell lymphoma expansion cohort after CAR T-cell therapy, and all patients with B-cell non-Hodgkin lymphoma from the dose-escalation and dose-expansion parts of the study were pooled for this preplanned analysis. Baseline characteristics and safety were analysed by dose group in patients who received any dose of the study drug (the safety analysis set). Activity endpoints were analysed by the subtype of B-cell non-Hodgkin lymphoma and dose group in patients who received any dose of study drug and had an opportunity to attend the response assessment at 12 weeks. For continuous variables, descriptive statistics were presented as the number of patients (%) or median (IQR, 95% CI, or range). For categorical or ordinal variables, frequencies and percentages were displayed for each category. For duration of response data, medians and 95% CIs were provided by the Kaplan–Meier method. Objective response rate and complete response rate were summarised with two-sided 95% exact binomial CIs using the Clopper–Pearson method. Patients who were not evaluable for best overall response were considered non-responders. Duration of response, duration of complete response (ie, time from first complete response to disease progression or death), and progression-free survival were analysed by Kaplan–Meier estimation. Patients without disease progression or death were censored at the last tumour assessment on or before the data cutoff date. Descriptive statistics were used to summarise odronextamab con centrations in serum over time.

A preliminary exposure–response analysis with logistic regression was conducted using best overall response data from patients with follicular lymphoma or diffuse large B-cell lymphoma who did not have previous CAR T-cell treatment following intravenous odronextamab (dose range 2–320 mg during dose escalation). This analysis evaluated the relationship between exposure metrics (average concentration [C_{avg}] or area under the curve [AUC] over time and pre-dose concentration at week 12 [C_{min}]), objective response rate, and complete response rate over 12 weeks of treatment. The accumulation ratios of odronextamab were calculated as median peak and trough concentrations at week 12 (steady state) divided by those at week 3.

All data were analysed using SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT02290951.

Role of the funding source

The study was sponsored and designed by employees of Regeneron Pharmaceuticals, in collaboration with the investigators. Data from the study were collected by investigators, analysed by statisticians employed by the sponsor, and interpreted by the authors (including employees of the sponsor). Medical writing support was provided and funded by the sponsor and all stages of manuscript development occurred under the guidance and supervision of the authors, who critically reviewed all drafts.

Results

From Feb 4, 2015, to Sept 25, 2021, 173 patients with CD20-positive relapsed or refractory B-cell non-Hodgkin lymphoma were assessed for eligibility and 28 were excluded (figure 1). 145 heavily pretreated and refractory patients were enrolled (94 to the dose-escalation and 51 to the dose-expansion part of the study). Patient demographics and baseline characteristics are summarised in table 1. The median age of patients was 67·0 years (IQR 57·0–73·0) and most were male (101 [70%] of 145).

At data cutoff (Sept 25, 2021), seven (5%) patients continued to receive treatment (all in the dose-expansion cohort), 33 (23%) completed treatment, and 105 (72%) discontinued treatment mainly due to progressive disease (63 [43%]; figure 1). Median duration of follow-up was 4·2 months (IQR 1·5–11·5). During dose escalation, odronextamab was administered up to the maximum dose of 320 mg once per week and no dose-limiting toxicities were observed. The maximum tolerated dose was not reached and there was no dose-dependent increase in toxic effects. Seven (5%) patients had retreatment with odronextamab, of whom three had follicular lymphoma, three had diffuse large B-cell lymphoma, and one had mantle cell lymphoma. Six of the retreated patients received doses less than 5 mg and one received 160 mg. All cases of retreatment were with the same original dose or at a higher cleared dose and occurred in patients in the dose-escalation phase of the study.

The number of patients included in each odronextamab dose level is shown in the appendix (p 8). Patients received a median of 10 doses (IQR 4–20) of odronextamab with a median 13·1 weeks (5·0–32·9) of exposure. The median relative dose intensity was 1·0 (1·0–1·0). Clinical activity was observed across all dose groups, increasing substantially in patients with follicular lymphoma grade 1–3a receiving odronextamab at 5 mg or higher (n=32) and in those with diffuse large B-cell lymphoma receiving odronextamab at 80 mg or higher (n=45).

Peak odronextamab serum concentrations were observed during the end of infusion or 4 h after infusion on week 1 (day 2) and week 2 (day 2) when doses were split. The pharmacokinetics profiles during the first 5 weeks of treatment and median trough concentration profiles up to 36 weeks are shown in the appendix (p 16). Median serum concentrations of odronextamab generally increased in a dose-dependent manner. Odronextamab showed non-linear pharmacokinetic properties with target-mediated drug

disposition. At full doses ranging from 12 mg to 320 mg between week 3 and week 12, the drug accumulation ratio with once per week dosing was up to 3·62 for median peak concentrations and from 1·81 to 5·31 for median trough concentrations.

A preliminary exposure–response analysis evaluated the association between odronextamab exposure and objective and complete response rates over 12 weeks using data from 40 patients with follicular lymphoma and 38 patients with diffuse large B-cell lymphoma who did not have previous CAR T-cell therapy (enrolled during dose escalation). Compared with C_{avg} and AUC, the C_{min} at week 12 provided the best correlation with a clinical response in these patients. Positive associations were observed between probability of objective or complete response rates and the C_{min} at week 12 in patients with follicular lymphoma and diffuse large B-cell lymphoma (appendix p 17), and the highest complete response rate was observed at doses of 80 mg or higher. On the basis of an evaluation of all available data, including safety, activity, pharmacokinetics, and exposure–response, the recommended dose selected for expansion in patients with relapsed or refractory follicular lymphoma grade 1–3a was 80 mg and the recommended dose selected for expansion in patients with relapsed or refractory diffuse large B-cell lymphoma was 160 mg.

All 145 patients had at least one treatment-emergent adverse event of any grade and 135 (93%) had at least one treatment-emergent adverse event related to treatment (table 2; appendix pp 11–13). Grade 3 or worse treatment-emergent adverse events occurred in 119 (82%) patients. The most common grade 3 or worse treatment-emergent adverse events were anaemia (36 [25%]), lymphopenia (28 [19%]), hypophosphataemia (27 [19%]), neutropenia (27 [19%]), and thrombocytopenia (20 [14%]). Treatment-emergent adverse events of special interest such as infections, infusion-related reactions, cytokine release syndrome, CNS or immune effector cell-associated neurotoxicity syndrome-like events, and tumour lysis syndrome are reported in the appendix (p 13).

71 (49%) patients had infections; 33 (23%) patients had grade 3 or worse infections, of which pneumonia (12 [8%]) was the most frequent. Most cytokine release syndrome events were grade 1 (52 [36%]) or grade 2 (27 [19%]). Grade 3 cytokine release syndrome events occurred in nine (6%) patients, and one (1%) patient with mantle cell lymphoma had a grade 4 cytokine release syndrome event in the context of grade 5 tumour lysis syndrome during dose expansion. Cytokine release syndrome was predominantly confined to cycle 1 (step-up dosing) and resolved within a median of 2 days (IQR 2–4) with supportive measures. All grade 3 or worse cytokine release syndrome events occurred before the optimisation of cytokine release syndrome risk mitigation during cycle 1. Of three patients receiving the optimised step-up regimen, two had grade 1 cytokine release syndrome and no grade 2 or worse cytokine release syndrome events were observed. Tocilizumab was used to manage grade 3 or worse cytokine release syndrome in seven (5%) patients and none had to discontinue treatment due to cytokine release syndrome. Immune effector cell-associated neurotoxicity syndrome-like events were noted in 18 (12%) patients, and four (3%) patients had grade 3 or worse events (including confusional state, somnolence, encephalopathy, aphasia, and cognitive disorder; n=1 for each; appendix p 13). Most of the neurological treatment-emergent adverse events were transient and resolved within a median of 3 days (IQR 1–7); none led to treatment discontinuation and there were no grade 4 or

5 immune effector cell-associated neurotoxicity syndrome-like events (appendix p 13; four events listed in the grade 3 or higher category are all grade 3 events).

Serious adverse events occurred in 89 (61%) of 145 patients; the most frequent were cytokine release syndrome (41 [28%]), pyrexia (11 [8%]), pneumonia (nine [6%]), and infusion-related reaction (six [4%]). 68 (47%) patients had a serious treatment-emergent adverse event in the first 4 weeks of treatment and in 88 (61%) patients a serious treatment-emergent adverse event necessitated prolonged or new hospitalisation.

70 (48%) patients had a treatment-emergent adverse event leading to treatment interruption or delay and in 14 (10%) these led to a dose reduction. 12 (8%) patients discontinued odronextamab due to a treatment-emergent adverse event. Ten treatment-emergent adverse events were considered treatment-related (grade 1 cytomegalovirus infection, grade 1 gait disorder, grade 3 haemolysis, grade 3 toxoplasmosis, grade 4 elevated aspartate aminotransferase, grade 5 tumour lysis syndrome; one of each; and grade 3 pneumonia and grade 3 fatigue; two of each) and three were unrelated to treatment (grade 3 neck abscess in a patient with previous spinal surgery, grade 3 device-related infection, and leukaemia; one of each).

20 patients died during treatment or within 90 days of the last dose. 13 of these deaths were due to disease progression, six due to adverse events, of which four were considered related to treatment (one patient with gastric involvement by lymphoma had a gastric perforation 6 days after the last dose, one had a lung infection after 22 days, one had pneumonia after 53 days, and one had tumour lysis syndrome after 3 days), and one due to relapse of a pre-existing solid tumour. Two deaths were considered unrelated to treatment by the investigator (one had a cardiac arrest after 23 days and one had COVID-19 after 34 days). In one patient, the primary cause of death was recurrence and progression of oesophagogastric cancer.

There were no additional safety signals among seven patients who underwent retreatment with odronextamab. The most frequent treatment-emergent adverse events among these patients were nausea (n=4), anaemia (n=3), and back pain (n=3). One patient had grade 1 cytokine release syndrome and four had grade 3 or higher treatment-emergent adverse events (hyponatraemia, hypophosphataemia, lymphopenia, and intervertebral disc protrusion; one of each). No serious or treatment-emergent adverse events leading to treatment discontinuation were reported in patients undergoing retreatment.

Antitumour activity was observed across all target dose groups (0·1–320 mg) and in all lymphoma subtypes (table 3; figure 2; appendix pp 14, 18). 142 (98%) of 145 patients were evaluable for activity and had an opportunity to attend a response assessment at week 12. Objective response rate was 51% (72 of 142; 95% CI 42–59) and the complete tumour response rate was 37% (52 of 142; 29–45; unpublished data on file with the sponsor).

In patients with follicular lymphoma who received odronextamab doses of 5 mg or higher, which was determined to be the active dose range for patients with indolent lymphoma, the objective response rate was 91% (29 of 32; 95% CI 75–98) and the complete response rate was 72% (23 of 32; 53–86; appendix p 14). Responses occurred early with a median

time to first complete response of 2·6 months (IQR 2·5–2·9) and median estimated duration of response of 15·8 months (95% CI 6·4–not estimable [NE]), with the longest complete response ongoing at 53·0 months (appendix p 14). The estimated probability of maintaining a complete response in 32 patients with follicular lymphoma who received odronextamab doses of 5 mg or higher was 60% (95% CI 34–79) at 12 months and 54% (28–74) at 48 months. The median progression-free survival was 17·1 months (7·5–NE; appendix p 19).

In patients with diffuse large B-cell lymphoma without previous CAR T-cell therapy who received odronextamab doses of 80 mg or higher, which was determined to be the active dose range for aggressive lymphoma, objective response rate was 53% (8 of 15; 95% CI 27–79), and all responses were complete responses (appendix p 14). The median time to first complete response was 2·3 months (IQR 1·0–2·7) and median duration of response was not reached (95% CI 2·9–NE), with the longest complete response ongoing at 32·4 months. In these patients, the estimated probability of maintaining a complete response at 12 months was 88% (95% CI 39–98) and at 24 months was 66% (95% CI 16–91). The median progression-free survival was 11·5 months (95% CI 0·5–NE; appendix p 19).

In patients with diffuse large B-cell lymphoma who had previous CAR T-cell therapy and received odronextamab doses of 80 mg or higher, the objective response rate was 33% (ten of 30; 95% CI 17–53) and complete response rate was 27% (eight of 30; 12–46; appendix p 14). The median time to complete response was 1·5 months (IQR 0·8–2·6) and median duration of response was not reached (95% CI 1·6–NE), with the longest complete response ongoing at 20·5 months. Importantly in this patient group, the estimated probability of maintaining a complete response at 12 months was 100% (95% CI NE–NE). The median progression-free survival was 2·0 months (95% CI 0·9–5·3; appendix p 19).

Patients who were retreated with odronextamab had no additional responses. Immunogenicity against odronextamab was low. Among 137 patients with B-cell non-Hodgkin lymphoma who had available anti-drug antibody data, one patient who received 2 mg of odronextamab had treatment-emergent anti-drug antibodies with a low titre at the final visit of safety follow-up (day 30 after the last dose; unpublished).

Discussion

In this first-in-human study, odronextamab monotherapy showed encouraging antitumour activity, robust durability of responses, and a manageable safety profile in the setting of heavily pretreated, highly refractory hard-to-treat patients with B-cell non-Hodgkin lymphoma. Step-up dosing was effective at mitigating the risk of cytokine release syndrome, which occurred predominantly during cycle 1 and resolved quickly. Most patients had full target dose exposure with minimal treatment delays. None of the patients had dose-limiting toxicities during dose escalation and the maximum tolerated dose was not reached. In patients with relapsed or refractory follicular lymphoma grade 1–3a, 80 mg was selected as the recommended dose for further expansion, and 160 mg was selected as the recommended dose for patients with relapsed or refractory diffuse large B-cell lymphoma. To our knowledge, this is the first study to report long-term treatment outcomes for a CD20×CD3

bispecific antibody with patients treated during dose-escalation and dose-expansion parts of the trial.

Early phase studies often enrol a diverse and heterogenous pool of patients. Overall, the baseline characteristics of patients enrolled in our study are generally consistent with those represented in contemporary trials of CD20×CD3 bispecific antibodies.[2,3] The patient population included older (≥65 years), heavily pretreated patients, most of whom were double refractory to previous alkylator and anti-CD20 therapy. However, one notable difference is that 29% of the patients enrolled in our study had received previous CAR T-cell therapy, which is considerably higher than the 2% seen with glofitamab and 9% seen with epcoritamab in recent studies.[2,3] As such, the patients included in this trial might have a particularly poor prognosis because they have been exposed to possible long-term toxic effects that are unique to CAR T-cell therapies and their associated preconditioning regimens. The proportion of patients with previous autologous haematopoietic stem-cell transplantation was 8%, which is lower than seen in other studies investigating CD20×CD3 bispecific antibodies;[2,3] however, this percentage could be partly explained by the older age and high refractory rate to chemotherapy noted in this patient population.

Acute immune reactions leading to transient cytokine release are a frequent side-effect of T-cell therapies.[2,14–18] Premedication with steroids and step-up dosing have been used to mitigate the occurrence of cytokine release syndrome after treatment with CD20×CD3 bispecific antibodies, regardless of the route of administration (intravenous or subcutaneous).[2,3,19,20] In our study, step-up dosing and additional prophylactic measures were systematically introduced and effectively mitigated the risk of cytokine release syndrome. In most cases, cytokine release syndrome was confined to cycle 1 with a low grade (1 or 2) and resolved with supportive care without sequelae. None of the patients discontinued treatment or had substantial treatment delays due to cytokine release syndrome. The frequency of grade 3 or worse cytokine release syndrome after intravenous treatment with odronextamab was 7% (all grade ≥3 cytokine release syndrome events occurred before optimisation of the step-up dosing schedule to include three steps during cycle 1). These observations are consistent with early findings from the ongoing phase 2 study of odronextamab mono therapy, which also implemented the same step-up regimen (NCT03888105). The reported rate of grade 3 or worse cytokine release syndrome is similar to the incidence reported with other intravenously administered CD20×CD3 bispecific antibodies. In a phase 1 study of intravenously administered glofitamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma, grade 3 or worse cytokine release syndrome was observed in 6% of patients who received the recommended phase 2 dose,[2] and the reported rates with intravenous mosunetuzumab, plamotamab, and IGM-2323 range between 1% and 6%.[20–23] Subcutaneous epcoritamab has also been investigated in patients with relapsed or refractory B-cell non-Hodgkin lymphoma and the phase 1/2 study reported no grade 3 or worse cytokine release syndrome events.[3] In our study, patients receiving odronextamab were admitted to hospital for observation during cycle 1 step-up dosing when cytokine release syndrome events most commonly occur. As data mature from ongoing studies implementing the recommended step-up regimen, the requirements for hospital admission might be reassessed and administration of odronextamab entirely within the outpatient setting might be feasible.

In patients with B-cell non-Hodgkin lymphoma, neurotoxicity has been observed with T-cell-engaging therapies. A phase 1 study of glofitamab reported immune effector cell-associated neurotoxicity syndrome-like events in 5% of patients using a sponsor-derived list of 12 terms[2] and the incidence of neurological symptoms in a phase 1/2 study of epcoritamab was 6%.[3] After treatment with odronextamab, CNS or immune effector cell-associated neurotoxicity syndrome-like events (as defined by a broad-term list) were primarily grade 1 or 2 and only four patients had a grade 3 event. No patients had grade 4 or 5 neurological treatment-emergent adverse events or discontinued odronextamab treatment due to such events. Since there are no standardised criteria for reporting immune effector cell-associated neurotoxicity syndrome-like events, the use of cross-study comparisons is somewhat limited.

There remains a high unmet need for safe, effective, and accessible treatment options for patients with relapsed or refractory B-cell non-Hodgkin lymphoma. CAR T-cell therapy is a foundational treatment in the management of such patients. However, many remain unsuitable candidates for CAR T-cell therapy upon relapse because they have a rapidly progressive phenotype, because of the requirements for apheresis, ex vivo genetic manipulation, and expansion of T cells, and because intensive preconditioning before dosing might lead to long-lasting cytopenias. The unmet need is amplified in patients who progress after CAR T-cell therapy, for whom prognosis remains dismal with salvage therapy.[24,25] This study provides evidence that odronextamab can confer durable, clinically relevant benefit for heavily pretreated patients with relapsed or refractory B-cell non-Hodgkin lymphoma, including for those who have progressed after CAR T-cell therapy.

Treatment with odronextamab at therapeutically relevant doses of 80 mg or higher was associated with an objective response rate of 53% (all complete responses) in patients with relapsed or refractory diffuse large B-cell lymphoma who did not have previous CAR T-cell therapy, with 88% of complete responses estimated to be ongoing at 12 months. Importantly, although objective response rate (33%) and complete response rate (27%) were lower in patients with diffuse large B-cell lymphoma who had progressed after previous CAR T-cell therapy, 100% of complete remissions were estimated to be ongoing at 12 months. These results might signal a clinically important advancement for patients after CAR T-cell therapy, for whom few options exist beyond salvage chemotherapy.

Early observations from dose-escalation studies with CD20×CD3 bispecific antibodies have been reported. Intravenous glofitamab has shown an objective response rate of 79% and complete response rate of 71% in 14 patients with relapsed or refractory diffuse large B-cell lymphoma treated at the recommended dose.[26] Subcutaneous epcoritamab has shown an objective response rate of 91% (95% CI 59–100) and complete response rate of 55% (95% CI 23–83) in 11 patients treated at doses of 48 mg and higher.[3] In a first-in-human study of plamotamab, the objective response rate in patients with non-Hodgkin lymphoma was 43% (95% CI 30–58), whereas for those with diffuse large B-cell lymphoma the rate was 38% (95% CI not available).[23] Preliminary data for IGM-2323 show an objective response rate of 31% in patients with diffuse large B-cell lymphoma.[21] Longer follow-up is required to assess the durability of responses and complete responses for these agents.

CAR T-cell therapy is an option for patients with follicular lymphoma who have progressed after at least two previous lines of therapy, which was supported by results from the single-arm ZUMA-5 study that showed an objective response rate of 91% (95% CI 83–96) and a complete response rate of 60% (95% CI 49–71) with axicabtagene ciloleucel.[27,28] In our study, odronextamab showed an objective response rate of 91% (95% CI 75–98) and a complete response rate of 72% (53–86) at doses of 5 mg or higher in patients with relapsed or refractory follicular lymphoma grade 1–3a, most of whom were heavily pretreated. Importantly, the rate of ongoing complete remission at 48 months was estimated to be 54%. To our knowledge, this is the first study of a CD20×CD3 bispecific antibody to show persistence of remissions in more than half of complete responders at 4 years. Odronextamab administration might offer an important off-the-shelf and convenient option for patients with relapsed or refractory follicular lymphoma who might be candidates for CAR T-cell therapy after progressing on two or more lines of therapy. Other early studies have reported results with CD20×CD3 bispecific antibodies in patients with relapsed or refractory follicular lymphoma.[3,22] Intravenous mosunetuzumab has shown an objective response rate of 79% (95% CI 69–87) and complete response rate of 58% (95% CI 47–68).[22] Early data from a first-in-human study of subcutaneous epcoritamab have shown an objective response rate of 90% (95% CI 55–100) and complete response rate of 50% (95% CI not available) in ten patients with evaluable relapsed or refractory follicular lymphoma.[3] Longer follow-up from these studies is awaited.

Patients treated in our study received a median of ten odronextamab doses, including the step-up doses. Although the treatment regimen was revised during dose expansion to allow treatment until progression, some patients had durable responses with a shorter duration of treatment. The optimal duration of therapy for this class of drug is yet to be determined. Whether the clinical outcomes differ between patients receiving limited cycles of therapy followed by an option of retreatment and those receiving continued therapy until progression remains unknown.[2,3,21–23] In our study, a subset of patients received limited cycles of treatment and seven patients were retreated upon progression, mostly at lower doses. None of the patients had a response upon retreatment. Although most patients received retreatment at low doses, a 2020 study[29] suggests that loss of CD20 might be associated with acquired resistance to odronextamab, which might partly explain an absence of observed activity on retreatment and support the recommended treatment paradigm of continued dosing. Further studies are required to delineate mechanisms of resistance for the class of CD20×CD3 bispecific antibodies to inform future clinical studies.

As with all phase 1 studies, the limitations of our study include the heterogeneous patient population, the small sample size, and the academic setting in which the study was conducted, which might preclude generalisability of the results to a broader population of patients with B-cell non-Hodgkin lymphoma. Additionally, patient follow-up was shorter in early protocol versions, which might lead to an underestimation of the durability of response. Although the objective response rate and duration of response are encouraging, whether these findings translate into a survival benefit is yet to be determined. Patients in our study were not consistently followed up for survival across the study and consequently, overall survival data could not be reported.

Development of the CD20×CD3 bispecific antibody drug class holds enormous potential to improve the lives of patients with B-cell non-Hodgkin lymphomas and is an area of focus in ongoing clinical trials. Odronextamab monotherapy is being investigated in a global phase 2 study in patients with relapsed or refractory B-cell non-Hodgkin lymphoma (NCT03888105) and subcutaneous administration in a first-in-human study (NCT02290951). Although the results reported to date show encouraging activity with a manageable tolerability profile, chemotherapy-free regimens combining odronextamab with other immune modulators, such as checkpoint inhibitors or costimulatory antibodies, might present an opportunity to improve outcomes for patients with hardest-to-treat B-cell non-Hodgkin lymphoma.

In summary, odronextamab has shown promising clinical activity, manageable safety, and durable responses in heavily pretreated, highly refractory patients with B-cell non-Hodgkin lymphomas. Odronextamab has the potential to provide off-the-shelf convenience for B-cell non-Hodgkin lymphoma patients, including those with rapidly progressive disease, and further investigation as monotherapy and in combination with other modalities is supported.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing

Qualified researchers can request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings in this study. Sharing individual anonymised participant data will be considered once odronextamab and its indication are approved by major health authorities (eg, Food and Drug Administration, European Medicines Agency, Pharmaceuticals, and Medical Devices Agency), if there is legal authority to share the data and no reasonable likelihood of participant reidentification. Requests should be submitted to https://vivli.org/.

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Research in context

Evidence before this study

Bispecific antibodies targeting CD20 on target B cells and CD3 on T cells are being developed as off-the-shelf immunotherapy for patients with B-cell non-Hodgkin lymphoma. We searched PubMed for articles published from database inception to Nov 10, 2021, using a string of search terms “CD20 AND CD3 AND bispecific AND antibody AND (lymphoma OR “B cell”)”, with no language restrictions. Of 49 results, 24 papers reported original research relevant to CD20×CD3 bispecific antibody therapies for lymphoma. 17 of these papers reported preclinical findings, eight of which were published between 2015 and 2021. Overall, CD20×CD3 bispecific antibodies showed effective binding to CD20-positive B cells and CD3-positive T cells, resulting in efficient and specific lysis of human B-cell lymphocytes and higher depletion than with rituximab. Potent tumour inhibitory activity and longer survival in mouse models were also reported, highlighting the potential of CD20×CD3 bispecific antibody therapies to become an alternative treatment option. Since 2015, two phase 1/2 studies of CD20×CD3 bispecific antibodies (glofitamab and epcoritamab) have been published. Both studies reported favourable clinical outcomes in heavily pretreated patients with relapsed or refractory B-cell non-Hodgkin lymphoma, showing objective response rates of 54% (glofitamab; n=171 patients), 68% (epcoritamab; 22 patients with diffuse large B-cell lymphoma), and 90% (epcoritamab; ten patients with follicular lymphoma). Durability data were limited by short follow-up periods in both studies (median <14 months). The most frequent adverse events included cytokine release syndrome, fever, fatigue, diarrhoea, neutropenia, anaemia, thrombocytopenia, and injection-site reactions. Cytokine release syndrome is a key safety consideration (eg, grade 3–4 events occurred in six [3·5%] of 171 patients in the glofitamab study), but is generally considered to be manageable. Phase 1/2 studies of monotherapy with three other bispecific antibodies (mosunetuzumab, plamotamab, and IGM-2323) for the treatment of patients with relapsed or refractory non-Hodgkin lymphoma have been presented as abstracts in the American Society of Hematology Annual Meeting. Objective response rates with mosunetuzumab (79–80% in patients with follicular lymphoma and 35% in those with aggressive non-Hodgkin lymphoma) were similar to those seen with glofitamab and epcoritamab, whereas for plamotamab they were lower (43% in all patients with non-Hodgkin lymphoma and 38% in those with diffuse large B-cell lymphoma). IGM-2323 is at an earlier phase of development, and initial data show objective response rates of 29% in patients with follicular lymphoma and 31% in those with diffuse large B-cell lymphoma.

Odronextamab is a fully human IgG4-based bispecific antibody that differs from other CD20×CD3 antibodies because of the minimal engineering and native antibody structure.

Added value of this study

We present results from the first-in-human study investigating odronextamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma. At longest follow-up of 4·5 years, our study is the first to report long-term patient outcomes with a CD20×CD3 bispecific antibody. We found that odronextamab had a manageable safety profile: there

were no dose-limiting toxicities, the maximum tolerated dose was not reached, and most patients had full target dose exposure with minimal treatment delays. Cytokine release syndrome and neurotoxicity were generally low grade and did not result in treatment discontinuation. Durable antitumour responses were observed across all dose groups in highly refractory patients with B-cell non-Hodgkin lymphoma, including those who had previously progressed following chimeric antigen receptor (CAR) T-cell therapy.

Implications of all the available evidence

Data from dose-escalation studies are often confounded by the inclusion of results from patients treated at suboptimal doses. This study provides preliminary validation of early activity signals previously observed with shorter follow-up. Additionally, activity has been observed in a group of 30 highly refractory patients with diffuse large B-cell lymphoma who have progressed following CAR T-cell therapy. To our knowledge, this study is the first to report durable remissions at 12 months in these patients, who would otherwise have a dismal prognosis. Overall, the early safety profile and encouraging antitumour activity support continued research and development of odronextamab. The dose-expansion portion of this study is ongoing, and recruitment is taking place for a global phase 2 trial of odronextamab monotherapy in patients with relapsed or refractory B-cell non-Hodgkin lymphoma (NCT03888105). Future phase 3 studies are also planned.

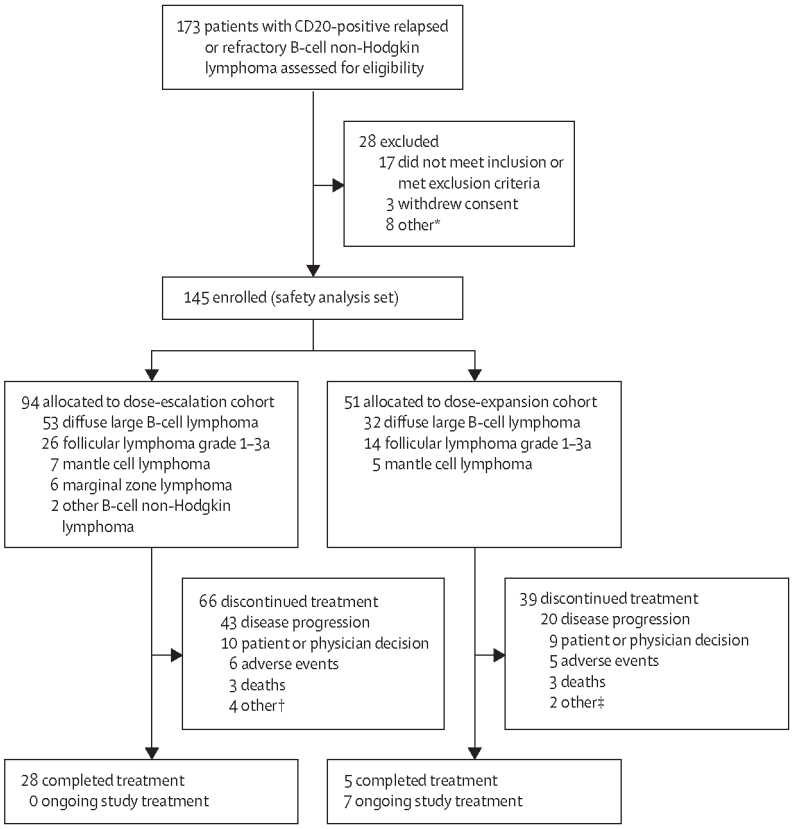

Figure 1: Trial profile.

*Death (n=1), investigator decision (n=2), patient decision (n=1), did not meet eligibility criteria (n=2), and enrolment was put on hold (n=2). †Suboptimal response to treatment (n=1), oesophagogastric cancer recurrence (n=1), and haematopoietic stem cell transplant (n=2). ‡Received radiation therapy (n=1) and missed one dose (n=1).

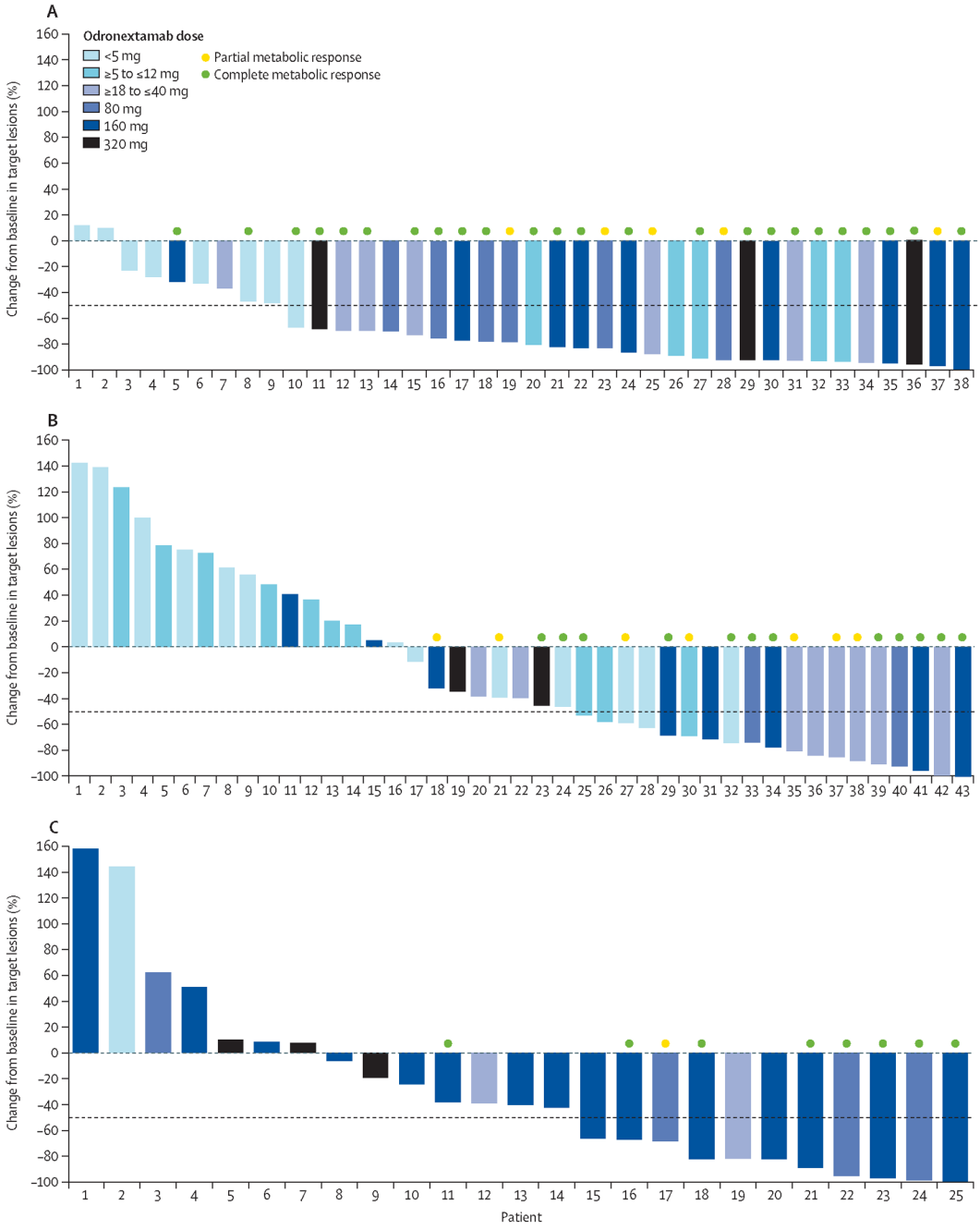

Figure 2: Best percentage change from baseline in target lesions

Data shown as best percentage change in activity in evaluable patients (ie, those attending assessment at week 12; all odronextamab doses) with relapsed or refractory follicular lymphoma grade 1–3a (A), diffuse large B-cell lymphoma without previous CAR T-cell therapy (B), and diffuse large B-cell lymphoma with previous CAR T-cell therapy (C). The dotted line indicates 50% change. CAR=chimeric antigen receptor.

Table 1:

Patient demographics and baseline characteristics

	Total (n=145)
Age	
Median	67·0 (57·0–73·0)
≥65 years	86 (59%)
<65 years	59 (41%)
Sex	
Male	101 (70%)
Female	44 (30%)
Race	
White	119 (82%)
Asian	11 (8%)
Unknown or not reported	7 (5%)
Black or African American	6 (4%)
Other	2 (1%)
Ethnicity	
Not Hispanic or Latino	132 (91%)
Hispanic or Latino	10 (7%)
Not reported	3 (2%)
ECOG performance status	
0	58 (40%)
1	87 (60%)
Ann Arbor stage at study entry	
I-II	21 (14%)
III-IV	123 (85%)
B-cell non-Hodgkin lymphoma diagnosis	
Diffuse large B-cell lymphoma	85 (59%)
Follicular lymphoma grade 1–3a	40 (28%)
Mantle cell lymphoma	12 (8%)
Marginal zone lymphoma	6 (4%)
Other *	2 (1%)
Bulky disease according to investigator assessment	49 (34%)
Median previous lines of therapy	3 (2–5)
Previous autologous haematopoietic stem-cell transplantation	12 (8%)
Previous CAR T-cell therapy	42 (29%) †
Refractory to last line of therapy	119 (82%)
Relapsed after last line of therapy	15 (10%)
Refractory to anti-CD20 antibody in any line	123 (85%)
Refractory to alkylator therapy in any line	102 (70%)
Double refractory to alkylator and anti-CD20 antibody in any line	100 (69%)

	Total (n=145)
Median time from end of last systemic therapy to first dose of odronextamab, months	2·8 (1·4–7·5)
Median time from start of last CAR T-cell therapy to first dose of odronextamab, months	6·0 (3·8–9·5)
Ratio of lactate dehydrogenase versus upper limit at baseline	
Aggressive lymphoma (n=86)	1·4 (0·9–2·1)
Diffuse large B-cell lymphoma (n=85)	1·4 (0·9–2·1)

Data are median (IQR) or n (%). CAR=chimeric antigen receptor.

*Includes follicular lymphoma grade 3b (n=1) and Waldenstrom macroglobulinaemia (n=1).

†Diffuse large B-cell lymphoma (n=35), follicular lymphoma grade 1–3a (n=4), and mantle cell lymphoma (n=3).

Table 2:

Treatment-emergent adverse events of any causality occurring in ≥10% of patients and grade 4 or 5 adverse events in all patients (n=145)

	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Pyrexia	105 (72%)	2 (1%)	0	0
Cytokine release syndrome	79 (54%)	9 (6%)	1 (1%)	0
Chills	67 (46%)	1 (1%)	0	0
Anaemia	19 (13%)	35 (24%)	1 (1%)	0
Fatigue	40 (28%)	7 (5%)	0	0
Hypophosphataemia*	15 (10%)	23 (16%)	4 (3%)	0
C-reactive protein increased	41 (28%)	0	0	0
Cough	40 (28%)	0	0	0
Hypotension	29 (20%)	7 (5%)	4 (3%)	0
Thrombocytopenia*	20 (14%)	11 (8%)	9 (6%)	0
Headache	36 (25%)	0	0	0
Nausea	34 (23%)	2 (1%)	0	0
Infusion-related reaction	32 (22%)	3 (2%)	0	0
Neutropenia*	8 (6%)	13 (9%)	14 (10%)	0
Decreased appetite	31 (21%)	3 (2%)	0	0
Lymphopenia*	4 (3%)	6 (4%)	22 (15%)	0
Dyspnoea	24 (17%)	7 (5%)	0	0
Blood creatinine increased	29 (20%)	1 (1%)	0	0
Oedema peripheral	30 (21%)	0	0	0
Tachycardia	27 (19%)	3 (2%)	0	0
Vomiting	28 (19%)	2 (1%)	0	0
Aspartate aminotransferase increased	15 (10%)	10 (7%)	4 (3%)	0
Diarrhoea	27 (19%)	2 (1%)	0	0
Leukopenia*	15 (10%)	9 (6%)	4 (3%)	0
Myalgia	27 (19%)	0	0	0
Alanine aminotransferase increased	16 (11%)	9 (6%)	1 (1%)	0
Insomnia	26 (18%)	0	0	0
Arthralgia	22 (15%)	2 (1%)	0	0
Back pain	23 (16%)	1 (1%)	0	0
Dizziness	23 (16%)	0	0	0
Abdominal pain	18 (12%)	4 (3%)	0	0
Constipation	20 (14%)	0	0	0
Hyperglycaemia	11 (8%)	7 (5%)	2 (1%)	0
Hypocalcaemia	17 (12%)	1 (1%)	1 (1%)	0
Hypoxia	11 (8%)	7 (5%)	1 (1%)	0
Hypoalbuminaemia	15 (10%)	2 (1%)	0	0
Hypomagnesaemia*	17 (12%)	0	0	0
Fibrin D dimer increased	16 (11%)	0	0	0

	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Pain in extremity	14 (10%)	2 (1%)	0	0
Pneumonia	3 (2%)	11 (8%)	0	1 (1%)
Sinus tachycardia	15 (10%)	0	0	0
Atrial fibrillation	5 (3%)	2 (1%)	1 (1%)	0
Aminotransferase increased	5 (3%)	2 (1%)	1 (1%)	0
Hyperuricaemia	2 (1%)	1 (1%)	1 (1%)	0
Pneumocystis jirovecii pneumonia	2 (1%)	1 (1%)	0	1 (1%)
Sepsis	0	0	2 (1%)	0
Acute respiratory failure	0	0	1 (1%)	0
Blood fibrinogen decreased	0	0	1 (1%)	0
Hyperphosphataemia	0	0	1 (1%)	0
Kidney rupture	0	0	1 (1%)	0
Urinary tract obstruction	0	0	1 (1%)	0
Cardiac arrest	0	0	0	1 (1%)
COVID-19	0	0	0	1 (1%)
Gastric perforation	0	0	0	1 (1%)
Toxoplasmosis	0	0	0	1 (1%)
Tumour lysis syndrome	0	0	0	1 (1%)

Data are n (%).

*Composite terms: hypomagnesaemia, hypophosphataemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia also include decreases in blood magnesium, blood phosphorus, white blood cell count, lymphocytes, neutrophils, and platelet count, respectively.

Table 3:

Investigator-assessed response in the overall population

	Relapsed or refractory follicular lymphoma grade 1–3a (n=40)	Relapsed or refractory diffuse large B-cell lymphoma without previous CAR T-cell therapy (n=49)	Relapsed or refractory diffuse large B-cell lymphoma with previous CAR T-cell therapy (n=33)	Mantle cell lymphoma (n=12)	Marginal zone lymphoma (n=6)	Other B-cell non-Hodgkin lymphoma (n=2)
Objective response (complete or partial)	31 (78%; 61·5–89·2)	19 (39%; 25·2–53·8)	11 (33%; 18·0–51·8)	6 (50%; 21·1–78·9)	4 (67%; 22·3–95·7)	1 (50%; 1·3–98·7)
Best overall complete tumour response	25 (63%; 45·8–77·3)	12 (24%; 13·3–38·9)	8 (24%; 11·1–42·3)	4 (33%; 9·9–65·1)	2 (33%; 4·3–77·7)	1 (50%; 1·3–98·7)
Best overall partial tumour response	6 (15%; 5·7–29·8)	7 (14%; 5·9–27·2)	3 (9%; 1·9–24·3)	2 (17%; 2·1–48·4)	2 (33%; 4·3–77·7)	0 (0·0–84·2)
Time to first response, months	1·2 (1·0–2·5)	1·4 (1·0–2·6)	1·1 (0·8–2·5)	1·0 (0·7–2·0)	1·2 (1·0–1·3)	1·8 (1·0–2·6)
Estimated duration of response, months	12·7 (95% CI 6·1-NE)	4·4 (95% CI 2·9-NE)	NR (95% CI 1·6-NE)	10·9 (95% CI 1·4-NE)	18·1 (95% CI 1·5-NE)	13·2 (95% CI NE-NE)
Observed duration of response, months	10·4 (4·4–19·9) *	4·4 (2·8–21·0) †	6·7 (1·6–12·8) ‡	7·6 (1·4–24·9)	9·8 (0·8–25·4)	13·2 (13·2–13·2)
Time to first complete response, months	2·6 (2·5–2·9)	2·3 (1·0–2·8)	1·5 (0·8–2·6)	1·3 (0·7–2·7)	2·5 (1·3–27)	1·8 (1·0–2·6)
Estimated duration of complete response, months	14·5 (95% CI 8·8-NE)	NR (95% CI 4·0-NE)	NR (95% CI NE-NE)	NR (95% CI 4·3-NE)	NR (95% CI 16·6-NE)	13·2 (95% CI NE-NE)
Observed duration of complete response, months	9·9 (3·9–19·9)	10·3 (4·2–21·4)	7·4 (2·6–15·8)	13·7 (2·2–30·1)	23·8 (16·6–31·1)	13·2 (13·2–13·2)

Data are n (%; 95% CI), median (IQR), or median (95% CI). CAR=chimeric antigen receptor. NE=not estimable. NR=not reached.

* Range 1·2–53·0+.

† Range 1·5–41·4+.

‡ Range 0·0+-20·5+ (plus sign denotes an ongoing response).