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ORIGINAL ARTICLE

Safety and efficacy of odronextamab in patients with relapsed or refractory follicular lymphoma☆

T. M. Kim[1]*, M. Taszner[2], S. Novelli[3], S-G. Cho[4], J. C. Villasboas[5], M. Merli[6], A. Jiménez-Ubieto[7], B. Tessoulin[8], L. M. Poon[9], D. Tucker[10], J. Walewski[11], S. Yi[12], Y. Song[13], G. Chong[14], E. Bachy[15,16], S. Guidez[17], A. Alonso[18], D. Jagadeesh[19], W. Zhang[20], L. Magnano[21,22], E. Iskierka-Jażdżewska[23], M. Tani[24], B. Shen[25], A. Uppala[25], M. Zhu[25], S. Shariff[26], J. Brouwer-Visser[25], A. Chaudhry[25], H. Mohamed[25], S. Ambati[25] & S. Luminari[27], on behalf of ELM-2 Investigators

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; [2]Department of Haematology and Transplantology, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland; [3]Hematology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [4]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; [5]Mayo Clinic, Rochester, USA; [6]Hematology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [7]Hematology Department, Hospital Universitario 12 de Octubre, Madrid, Spain; [8]Hematology Department, Nantes University Hospital, Nantes, France; [9]Hematology Oncology National University Hospital, Singapore, Singapore; [10]Department of Hematology, Royal Cornwall Hospital, Truro, UK; [11]Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie Państwowy Instytut Badawczy, Warsaw, Poland; [12]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; [13]Department of Lymphoma, Peking University Cancer Hospital & Institute (Beijing Cancer Hospital), Beijing, China; [14]Department of Medical Oncology, and Clinical Haematology, Olivia Newton-John Cancer Centre, Heidelberg, Australia; [15]Department of Hematology, Lyon Sud Hospital, Lyon, France; [16]Lymphoma Immuno-Biology (LIB) team, Inserm U1111, CIRI, Lyon, France; [17]Centre Hospitalier Universitaire (CHU) de Poitiers, Poitiers, France; [18]Hospital Universitario Quiron Salud Madrid, Madrid, Spain; [19]Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, USA; [20]Hematology Department, Peking Union Medical College Hospital, Beijing, China; [21]Hematology Department, Hospital Clínic of Barcelona, Barcelona, Spain; [22]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [23]Copernicus Memorial Hospital, Department of General Hematology, Medical University of Łódź, Łódź, Poland; [24]Hematology Unit, Santa Maria delle Croci Hospital, Ravenna, Italy; [25]Regeneron Pharmaceuticals, Inc., Tarrytown, USA; [26]Regeneron UK Ltd., Uxbridge, UK; [27]Division of Hematology, Azienda Unità Sanitaria Locale-IRCCS, Reggio Emilia, Italy

Available online 13 August 2024

Background: Odronextamab, a CD20×CD3 bispecific antibody that engages cytotoxic T cells to destroy malignant B cells, has demonstrated encouraging activity across multiple subtypes of relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma.

Patients and methods: This phase II study (ELM-2; NCT03888105) evaluated odronextamab in patients with R/R follicular lymphoma after two or more lines of systemic therapy. Patients received intravenous odronextamab in 21-day cycles, with step-up dosing in cycle 1 to help mitigate the risk of cytokine release syndrome, until disease progression or unacceptable toxicity. The primary endpoint was objective response rate by independent central review.

Results: Among 128 patients evaluated, 95% completed cycle 1, and 85% completed four or more cycles. At 20.1 months' efficacy follow-up, objective response rate was 80.0% and complete response rate was 73.4%. Median duration of complete response was 25.1 months. Median progression-free survival was 20.7 months, and median overall survival was not reached. Discontinuation of odronextamab due to adverse events occurred in 16% of patients. The most common treatment-emergent adverse events were cytokine release syndrome [56%; grade ≥3 1.7% (1/60) with 0.7/4/20 mg step-up], neutropenia (39%), and pyrexia (38%).

Conclusions: Odronextamab achieved high complete response rates with generally manageable safety in patients with heavily pretreated R/R follicular lymphoma.

Key words: follicular lymphoma, bispecific antibody, odronextamab, clinical trial

INTRODUCTION

Follicular lymphoma (FL) is the most common type of indolent non-Hodgkin lymphoma (NHL).[1,2] Chemo-immunotherapy with an anti-CD20 antibody is the basis of treatment for FL, yet patients will invariably relapse. Outcomes worsen after each successive relapse,[3,4] indicating the need for effective treatments for patients with relapsed or refractory (R/R) FL. T-cell—engaging therapies represent an important advance, with chimeric antigen receptor T-cell (CAR T) therapies (axicabtagene ciloleucel, tisagenlecleucel,

*Correspondence to: Prof Tae Min Kim, Seoul National University Cancer Research Institute, Seoul, 03080, South Korea. Tel: +82-2-2072-3559
E-mail: gabriel9@snu.ac.kr (T. M. Kim).

☆Note: This study was previously presented as first interim analysis at the American Society of Hematology (ASH) Annual Meeting and Exposition, 10-13 December 2022, New Orleans, LA, USA (Kim TM, et al. Oral presentation #949). Primary analysis most recently presented at the European Hematology Association (EHA) Hybrid Congress, 13-16 June 2024, Madrid, Spain (Taszner M, et al. Oral presentation S232).

and lisocabtagene maraleucel) and two bispecific antibodies (mosunetuzumab and epcoritamab) currently recommended as treatment options at the third line and beyond for R/R FL.[5] Whilst CAR-T therapies have demonstrated impressive efficacy in patients with R/R B-cell NHL (B-NHL), their use can be limited by access, eligibility, tolerability, manufacturing time, cost, and potential risk of secondary malignancies.[6-9] In comparison, bispecific antibodies are a readily available, accessible option for off-the-shelf administration.

Odronextamab is an off-the-shelf, human CD20×CD3 bispecific antibody that simultaneously engages cytotoxic T cells and malignant B cells, resulting in malignant cell death.[10,11] The ELM-1 phase I, dose-escalation/expansion study (NCT02290951) in heavily pretreated B-NHL subtypes demonstrated that odronextamab was active at doses ≥5 mg in indolent lymphoma; the objective response rate (ORR) was 91% and the complete response (CR) rate was 72% in patients with FL grade 1-3a.[10] Here, we report the primary analysis of odronextamab in patients with R/R FL from the ELM-2 phase II study.

PATIENTS AND METHODS

Study design

ELM-2 (NCT03888105) is a phase II, open-label, multicohort, multicenter study of odronextamab monotherapy for patients with R/R B-NHL. Patients were recruited from multiple centers from the USA, Australia, Canada, China, France, Germany, Italy, Japan, the Republic of Korea, Poland, Singapore, Spain, Taiwan, and the UK. The study protocol and amendments were approved by the relevant institutional review boards and ethics committees. The study was conducted in accordance with applicable regulatory requirements, guidelines of Good Clinical Practice specified by the International Conference on Harmonization (ICH E6), and principles originating from the Declaration of Helsinki. Data were analyzed by the investigators and sponsor statisticians, and interpreted by authors. Written informed consent was obtained from all participants.

Patients

For the FL cohort, patients were aged ≥18 years, had FL grade 1-3a with central histopathologic confirmation, and were refractory to or had relapsed after two or more prior lines of systemic therapy, including an anti-CD20 antibody and alkylator. Patients must have failed or been considered unsuitable for rituximab-lenalidomide (R^2). All patients had measurable disease on cross-sectional imaging, Eastern Cooperative Oncology Group performance status 0-1, and adequate bone marrow, hepatic, and renal function. Patients with primary central nervous system lymphoma or who had received prior allogeneic stem cell transplant, CAR-T therapy, or treatment with a CD20×CD3 bispecific antibody were excluded.

Measures to ensure diverse and inclusive enrollment included: diverse trial sites; translated consent forms for under-represented populations; extended screening windows for patients with access constraints; broad eligibility criteria to include patients with controlled human immunodeficiency virus (HIV), hepatitis B, and hepatitis C; and lower thresholds for those with compromised organ function due to lymphoma.

Study treatment

Patients received intravenous (i.v.) odronextamab in 21-day cycles. Step-up dosing was implemented in cycle (C) 1 to help mitigate the risk of cytokine release syndrome (CRS), followed by odronextamab 80 mg on day (D) 1, 8, and 15 in C2-4. Maintenance dosing of odronextamab 160 mg every 2 weeks (Q2W) continued until disease progression or another protocol-defined reason for treatment discontinuation. In patients with CR lasting ≥9 months (investigator evaluation), dosing frequency was reduced to 160 mg every 4 weeks (Q4W).

The step-up regimen was optimized during the study (Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2024.08.2239) to further reduce the risk of severe CRS, and consisted of 0.7/4/20 mg administered as 0.2 mg and 0.5 mg on C1D1 and C1D2, 2 mg each on C1D8 and C1D9, and 10 mg each on C1D15 and C1D16. Patients were admitted for inpatient monitoring for 24 h following each infusion up to and including C2D1. Premedication, including steroid prophylaxis, was administered throughout step-up dosing to reduce CRS risk (Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2024.08.2239). Prophylaxis for *Pneumocystis jirovecii* pneumonia was recommended for all patients. Anti-infection prophylaxis also included i.v. immunoglobulin supplementation and antivirals (Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2024.08.2239).

Outcomes

The primary endpoint was ORR (based on best overall response), assessed by independent central review (ICR) according to the Lugano criteria,[12] with first assessment at week 12. Secondary endpoints included ORR per local investigator assessment, CR rate, duration of response (DOR), progression-free survival (PFS), overall survival (OS), patient-reported outcomes (PROs), and pharmacokinetics. Exploratory endpoints included biomarker analyses, such as minimal residual disease (MRD) status and CD20 expression.

Disease assessments [using computed tomography (CT)/magnetic resonance imaging (MRI), and positron emission tomography] were carried out during screening, at week 12, then every 8 weeks in year 1, every 12 weeks in year 2, and during follow-up. A diagnostic quality MRI or CT scan with contrast of the neck, chest, abdomen, and pelvis, and any other known sites of disease, could be carried out at any time when disease progression was expected. For each patient, the same method of measurement and the same technique were used to evaluate each lesion throughout the study.

For MRD assessment, whole blood was collected in Streck tubes which were processed to separate out the

Buffy coat containing blood cells and the supernatant containing the circulating tumor DNA. The Buffy coat was used as a germline control to filter out germline variants. Samples were taken at baseline and from C4D15. For MRD assessment, circulating tumor DNA was measured using a modified AVENIO assay (Roche, Basel, Switzerland; research only) with next-generation sequencing, based on the cancer personalized profiling by deep sequencing technique.[13] MRD clearance was reported when the *P* value for allele frequency was >0.005.[14]

CD20 expression was assessed in baseline biopsies using full automated chromogenic immunohistochemistry assays at a central laboratory. CD20 was detected with a rabbit monoclonal primary antibody (clone SP32; Abcam, Cambridge, UK) and a secondary horseradish peroxidase—conjugated antibody.

Safety and tolerability were assessed throughout the study and during safety follow-up. Adverse events (AEs) were recorded for up to 90 days after the last odronextamab dose or until initiation of another anti-lymphoma therapy and were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0); CRS was graded according to the American Society for Transplantation and Cellular Therapy criteria.[15]

Statistical analyses

This study was designed to include up to 128 patients with FL, with ≥60 patients receiving the revised 0.7/4/20 mg step-up regimen. An exact binomial design was adopted for the primary endpoint, and patients not assessable for best overall response were considered non-responders. Final analysis for the primary endpoint was carried out when all patients had completed the 52-week assessment or withdrawn from the study. Efficacy and safety analyses were carried out in all patients who received at least one dose of odronextamab. Duration of efficacy follow-up was calculated based on reverse Kaplan—Meier PFS (investigator assessment). DOR, PFS, and OS were analyzed using the Kaplan—Meier estimation method.

RESULTS

Patients

At data cut-off (20 October 2023), 128 patients with R/R FL had enrolled at 49 sites between 18 December 2019 and 27 July 2022 (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.08.2239). Patients had completed a median of 19.4 treatment cycles (range, 0.1-90.5 cycles), with 95% completing C1 and 85% completing four or more cycles. Twenty-nine patients (23%) remained on treatment at data cut-off. The most common reasons for treatment discontinuation were disease progression (25%), AEs (16%), death (all due to AEs), physician decision, and patient withdrawal (each 10%).

At baseline, median population age was 61.0 years (range, 22-84 years), and the majority of patients had advanced-stage disease (Ann Arbor stage III-IV, 85%; Table 1). Patients had received a median of three prior lines of therapy (range, 2-13), with 92 (72%) refractory to their last line of therapy. Approximately three-quarters of patients (74%) were refractory to an anti-CD20 antibody treatment, 41% were double-refractory to an anti-CD20 antibody and an alkylator, and 49% had progressive disease within 24 months of first-line treatment (POD24). In addition, 39 patients (30%) had received prior autologous stem-cell transplant (ASCT).

Table 1. Patient demographics and baseline characteristics

Characteristic	*N* = 128
Median age (range), years	61.0 (22-84)
Aged ≥75 years, *n* (%)	12 (9)
Male sex, *n* (%)	68 (53)
Race, *n* (%)	
White	79 (62)
Asian	34 (27)
Other	1 (1)
Unknown/not reported	14 (11)
Geographic region, *n* (%)	
Asia-Pacific	41 (32)
Europe	70 (55)
North America	17 (13)
Eastern Cooperative Oncology Group performance status, *n* (%)	
0	65 (51)
1	62 (48)
2[a]	1 (1)
Ann Arbor stage III-IV, *n* (%)	109 (85)
FLIPI risk score, *n* (%)	
Low (0-1)	21 (16)
Intermediate (2)	33 (26)
High (3-5)	74 (58)
Bulky disease, investigator assessment, *n* (%)	18 (14)
Median prior lines of therapy (range), *n (%)*	3 (2-13)
≥3 prior lines	69 (53.9)
≥4 prior lines	44 (34.4)
≥5 prior lines	22 (17.2)
Prior PI3K inhibitor, *n* (%)	18 (14)
Prior rituximab-lenalidomide, *n* (%)	17 (13)
Prior ASCT, *n* (%)	39 (30)
Refractory to last line of therapy, *n* (%)	92 (72)
Refractory to anti-CD20 antibody, *n* (%)	95 (74)
Double refractory to alkylator/anti-CD20 antibody, *n* (%)	53 (41)
POD24, *n* (%)	63 (49)

ASCT, autologous stem-cell transplant; FLIPI, Follicular Lymphoma International Prognostic Index; PI3K, phosphoinositide 3-kinase; POD24, progression of disease within 24 months of first-line treatment.
[a]Patient included who did not meet eligibility criteria of Eastern Cooperative Oncology Group performance status 0-1.

Efficacy

At data cut-off, median duration of efficacy follow-up was 20.1 months. The primary endpoint of ORR by ICR was 80% [103/128; 95% confidence interval (CI) 72.5%-86.9%; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.08.2239], and the CR rate was 73%; >90% of responders achieved CR. ORR and CR rate per local investigator were 82% and 73%, respectively. Reduction in tumor size was recorded in 95% of evaluable patients (Figure 1).

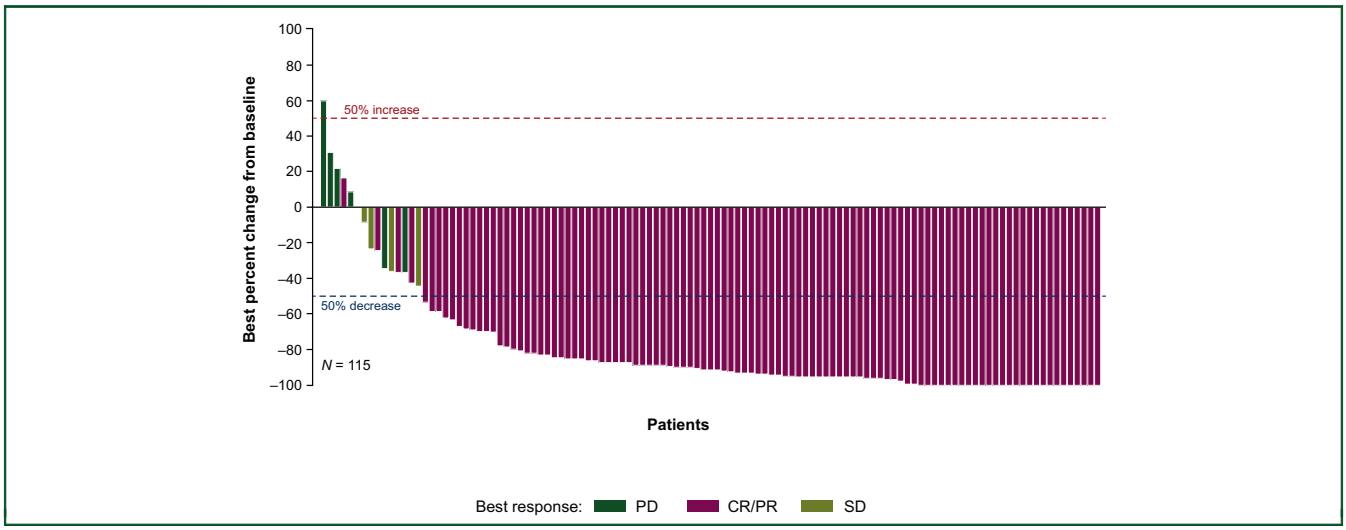

Figure 1. Waterfall plot of best percent change from baseline in tumor SPD. Data for each evaluable patient are shown as a separate bar on the figure. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; SPD, sum of the products of the diameters.

By week 12 (first planned assessment), 91/103 responders (88%) had achieved at least partial response (PR). Five patients with PR converted to CR [two had stable disease (SD) at initial assessment], and one patient with SD converted to CR, all before 28 weeks of treatment. Overall, the median time to first response was 2.7 months (range, 1.8-7.9 months). Median DOR was 22.6 months, and median duration of CR was 25.1 months (Figure 2). The probability of maintaining CR for 12 months was 75.0%.

Odronextamab demonstrated efficacy across all prespecified subgroups, with consistent effects in high-risk patients (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2024.08.2239), including those with POD24 (ORR, 81%; CR rate, 73%) and prior ASCT (ORR, 85%; CR rate, 77%), and those who had received four or more (ORR, 73%; CR rate, 66%) and five or more (ORR, 64%; CR rate, 59%) prior lines of therapy. Among 45 patients who transitioned from Q2W to Q4W dosing, 31 remained in response at data cut-off [median DOR from time of transition, 22.8 months (95% CI 11.2 months-not evaluable)].

Median PFS was 20.7 months, with 12-, 18-, and 24-month PFS rates of 66.2%, 57.5%, and 46.1%, respectively (Figure 3A). Median OS was not reached, and 12- and 24-month OS rates were 86.2% and 70.1%, respectively (Figure 3B). Median PFS and OS were greater in patients with CR versus PR (PFS, 27.8 versus 11.3 months; OS, not reached versus 18.4 months) (Figure 3).

Biomarker assessment and characterization of immune cells

The prognostic impact of MRD was assessed in 64 patients who had paired samples at baseline and C4D15. PFS was longer in patients who were MRD-negative versus MRD-positive at C4D15 (hazard ratio 0.26; 95% CI 0.10-0.66) (Figure 3C), and among evaluable patients who discontinued from the study due to disease progression ($n = 14$), none achieved MRD-negative status on or after C4D15.

Robust B-cell depletion was observed at C2D8, which was sustained through treatment and follow-up (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2024.08.2239). There was a trend toward increased T-cell levels (CD3+, CD4+, or CD8+ cells) from baseline through C5D8 (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2024.08.2239). A transient elevation of key cytokines interferon-γ and interleukin-6 was observed in patients who utilized 0.7/4/20 mg step-up dosing, predominantly during C1 (Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2024.08.2239).

Response was evaluated according to baseline CD20 protein expression in patients with tissue evaluable for CD20 immunohistochemistry ($n = 71$). Odronextamab treatment was associated with clinical responses irrespective of baseline CD20 expression level, with CRs recorded even in patients who had no, or low proportions of, CD20-positive cells detected in their samples (Supplementary Figure S6, available at https://doi.org/10.1016/j.annonc.2024.08.2239).

Pharmacokinetics

Pharmacokinetics analysis revealed an increase in odronextamab exposure through C1 step-up and C2-4 (Supplementary Figure S7A, available at https://doi.org/10.1016/j.annonc.2024.08.2239). Once the first full dose was administered at C2D1, mean (standard deviation) odronextamab exposure was independent of prior step-up regimens administered (Supplementary Figure S7A, available at https://doi.org/10.1016/j.annonc.2024.08.2239). Efficacious odronextamab concentrations were maintained through 80 mg weekly and 160 mg Q2W dosing, and in patients who switched to Q4W dosing (Supplementary Figure S7B, available at https://doi.org/10.1016/j.annonc.2024.08.2239). Population pharmacokinetics analysis

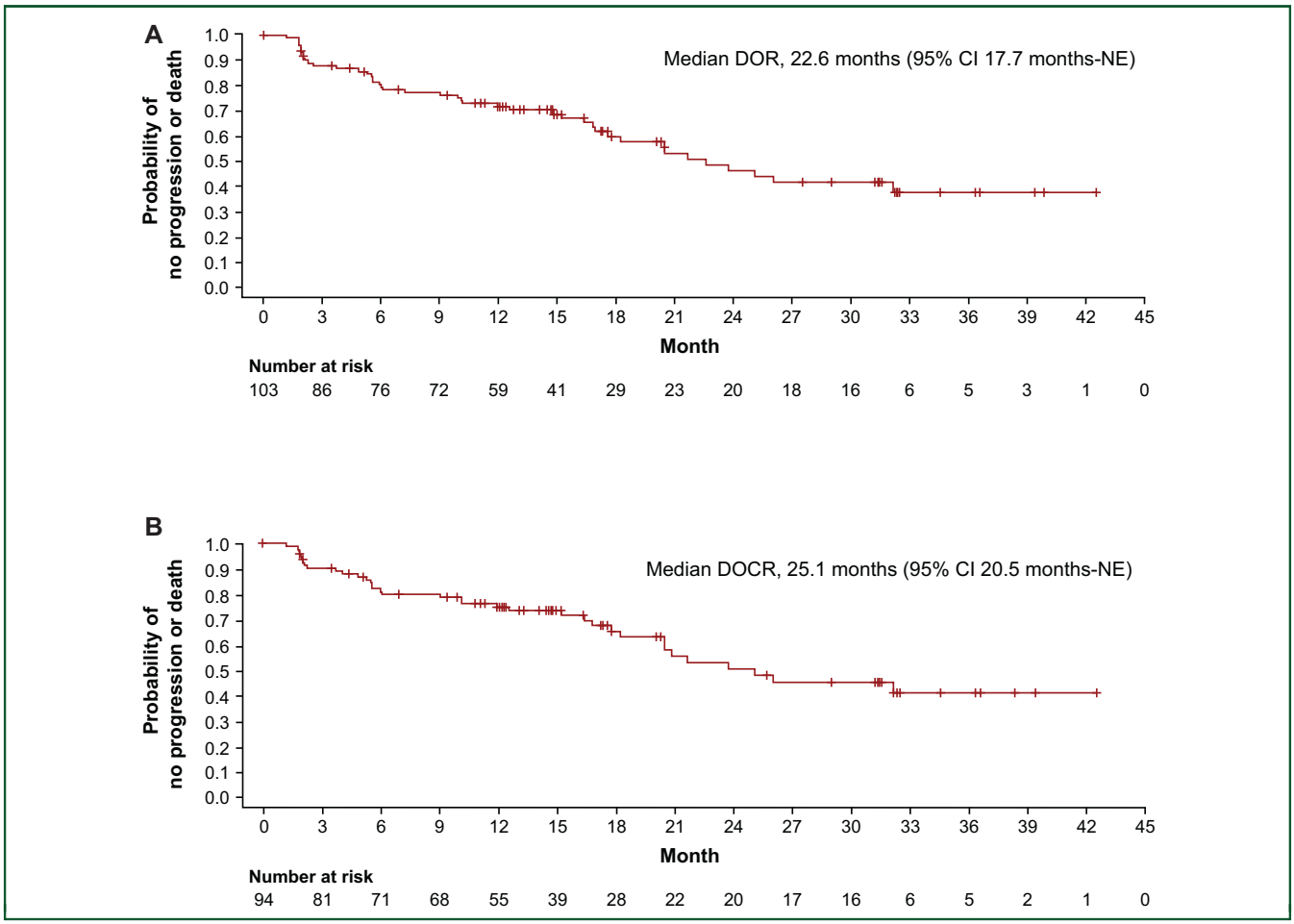

Figure 2. DOR and DOCR with odronextamab, assessed by independent central review. (A) DOR and (B) DOCR kaplan-meier curves are shown, including median values with 95% CIs.

showed odronextamab clearance was target-mediated, and dependent on concentration and time.[16]

Safety

Treatment-emergent AEs (TEAEs) occurred in all patients, with 118 patients (92%) experiencing at least one treatment-related TEAE (Table 2). The most common any-grade TEAEs were CRS (56%), neutropenia (39%), and pyrexia (38%), and the most common grade 3 or 4 TEAEs were neutropenia (32%), anemia, and neutrophil count decreased (both 12%). TEAEs led to dose interruption/delay in 107 patients (84%), dose reduction in 12 patients (9%), and treatment discontinuation in 20 patients (16%) (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.08.2239). Treatment-related TEAEs that led to treatment discontinuation were infusion-related reaction ($n = 2$), pneumonia, viral bronchitis, pseudomonal pneumonia, progressive multifocal leukoencephalopathy (PML), frontal lobe epilepsy, weight decreased, arthralgia ($n = 1$ each), and tremor plus infusion-related reaction in one patient. Treatment-related grade 5 TEAEs occurred in four patients: pneumonia, PML, pseudomonal pneumonia, and COVID-19 pneumonia plus systemic mycosis ($n = 1$ each).

AEs of special interest included CRS, neurologic events, infusion-related reactions, tumor lysis syndrome, and infections (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.08.2239). CRS was reported in 34 patients (57%) who received the 0.7/4/20 mg regimen (grade 1, $n = 27$; grade 2, $n = 6$; grade 3, $n = 1$). CRS mostly occurred during step-up dosing [of patients who developed CRS, 97% (33/34) developed CRS before the second full dose; eight patients had CRS following the second full dose (Supplementary Figure S8, available at https://doi.org/10.1016/j.annonc.2024.08.2239)], with median time to onset of 19.7 h (range, 0.7-159.0 h). All events resolved within a median of 7.7 h (range, 0.6-184.0 h); CRS was primarily managed by systemic steroids or tocilizumab (in 33% and 17% of patients, respectively) (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2024.08.2239). There was one grade 2 immune effector cell-associated neurotoxicity syndrome (ICANS) event (0.7/4/20 mg step-up regimen), which was not associated with CRS and resolved without sequelae. One patient who received the 0.7/4/20 mg step-up regimen had low-grade tumor flare. Infection TEAEs occurred in 80% (grade 3, 28%; grade 4, 3%) of patients (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2024.08.2239), leading to

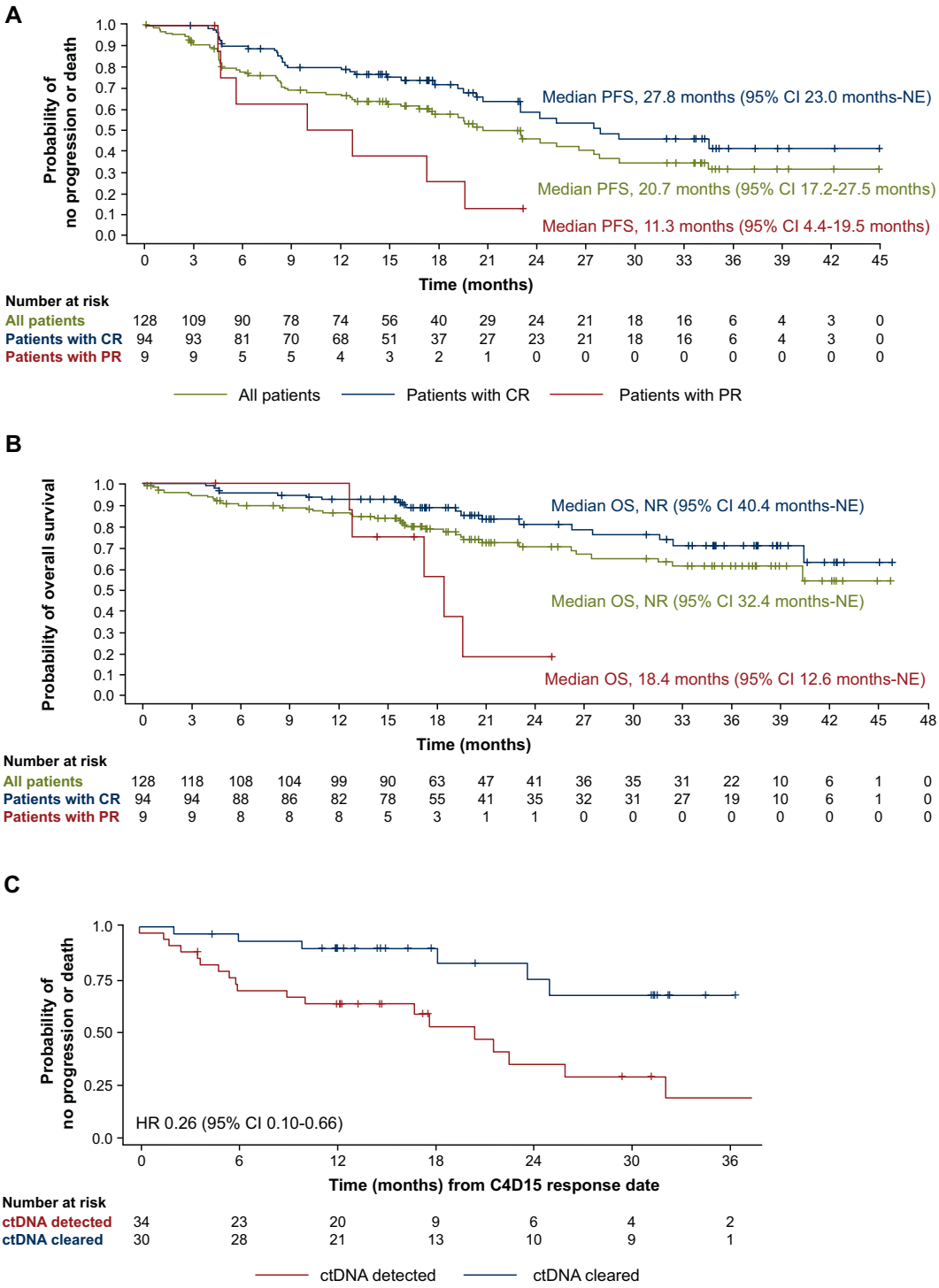

Figure 3. PFS and OS in patients treated with odronextamab. (A) PFS and (B) OS for all patients, and by best overall response. (C) PFS according to MRD clearance at C4D15 in MRD-evaluable patients. HR for PFS in ctDNA detected versus ctDNA cleared was calculated by univariate Cox regression.
C4D15, cycle 4 day 15; CI, confidence interval; CR, complete response; ctDNA, circulating tumor DNA; HR, hazard ratio; MRD, minimal residual disease; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response.

dose interruption/delay in 57% of patients and treatment discontinuation in 9% of patients. Infections were observed during the course of the treatment, with the rate of occurrence of treatment-emergent infections being stable from ∼15 months (Supplementary Figure S9, available at https://doi.org/10.1016/j.annonc.2024.08.2239).

Pneumocystis jirovecii pneumonia was observed in two patients, neither of whom had received prophylaxis. In patients with severe hypogammaglobulinemia (<400 mg/dl), there was a trend toward reduced opportunistic infection in those with [1/10 (10%)] versus without [8/44 (18%)] i.v. immunoglobulin supplementation. COVID-19 was

Table 2. Summary of TEAEs with odronextamab treatment

Event, preferred term[a], *n* (%)	*N* = 128	
	Any event	Treatment-related
Any TEAE	128 (100)	118 (92.2)
TEAEs occurring in >15% of patients		
CRS	72 (56.3)	72 (56.3)
Neutropenia	50 (39.1)	39 (30.5)
Pyrexia	48 (37.5)	31 (24.2)
Anemia	43 (33.6)	26 (20.3)
COVID-19	41 (32.0)	5 (3.9)
Infusion-related reaction	39 (30.5)	37 (28.9)
Diarrhea	36 (28.1)	12 (9.4)
Arthralgia	28 (21.9)	13 (10.2)
Hypokalemia	28 (21.9)	9 (7.0)
Nausea	25 (19.5)	13 (10.2)
Headache	24 (18.8)	13 (10.2)
Fatigue	24 (18.8)	17 (13.3)
Rash	23 (18.0)	15 (11.7)
Constipation	23 (18.0)	4 (3.1)
Alanine aminotransferase increased	23 (18.0)	18 (14.1)
Cough	20 (15.6)	4 (3.1)
Any grade 3 or higher TEAE	110 (85.9)	82 (64.1)
Serious TEAEs	87 (68.0)	57 (44.5)
TEAE leading to treatment discontinuation	20 (15.6)	10 (7.8)
TEAE leading to death	18 (14.1)	4 (3.1)

ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.
[a]Preferred term according to the NCI CTCAE (version 5.0), except for CRS, which was graded per ASTCT criteria.[15]

reported in 37% of patients (grade 5, 6%); non-COVID-19 grade 5 infections were pneumonia ($n = 3$), sepsis, systemic mycosis, PML, pseudomonal pneumonia, and *Escherichia* sepsis ($n = 1$ each).

DISCUSSION

In this study, odronextamab treatment achieved deep and durable responses in heavily pretreated patients with R/R FL and demonstrated a generally manageable safety profile. These data are consistent with those from patients with R/R FL in the ELM-1 study[10] and with results reported in patients with R/R diffuse large B-cell lymphoma,[17] supporting the potential of odronextamab for management of indolent and aggressive B-NHL.

CR is an important treatment goal in R/R FL, as it consistently translates into long-term survival benefits. In studies of approved T-cell-engaging therapies, the probability of maintaining response at 12 months was greater among patients achieving CR versus PR.[18-20] In this study, odronextamab achieved an ORR of 80% and CR rate of 73%. Although differences between studies prohibit cross-trial comparisons, for reference, the CR rates reported in pivotal studies of anti-CD19 CAR-T therapies in R/R FL were 69%-79%.[19,20] Of the other recommended third-line FL treatments, CR rates were 13% (in *EZH2*-mutant FL) with tazemetostat,[21] 39% with zanubrutinib plus obinutuzumab,[22] 14% with copanlisib,[23] 60% with mosunetuzumab,[18] and 63% with epcoritamab.[24] The median duration of CR with odronextamab was >2 years, and achieving CR versus PR translated to substantially longer PFS and OS.

Patients enrolled in the ELM-2 FL cohort represent a particularly refractory, hard-to-treat population. Approximately one-third had received four or more prior lines of therapy, 30% had prior ASCT, and 74% were refractory to an anti-CD20 antibody; CR rates in these subgroups were 66%, 77%, and 69%, respectively. Tumor response to odronextamab was not associated with baseline CD20 expression, unlike other CD20×CD3 bispecific antibodies which did not show clinical activity in patients with low (<10%) CD20 levels.[25] MRD clearance was strongly associated with clinical outcomes, and no evaluable patients who discontinued due to disease progression had achieved MRD clearance on or after C4D15. These data support insights from other studies suggesting MRD may be a relevant biomarker in R/R FL,[26,27] although validation from future studies is required.

Continued odronextamab treatment was adopted to retain suppression of tumor growth, and for patient convenience, dosing frequency was reduced to Q4W in patients with durable CR (≥9 months). Effective drug concentrations were achieved with this approach, and the durability associated with odronextamab response was preserved (median DOR after transition to Q4W was 22.8 months). Patients receiving odronextamab in ELM-2 reported that they maintained good quality of life and functioning (EORTC QLQ-C30 questionnaire), with least square mean changes remaining below the published thresholds for clinically important worsening.[28] Additionally, >60% of patients reported maintenance or clinically meaningful improvement in PROs (FACT-Lym LymS and EQ-5D-3L-VAS scales) from baseline at each assessment during 50 weeks of odronextamab treatment,[28] thus supporting the feasibility of this regimen.

Odronextamab demonstrated a generally manageable safety profile, with 95% of patients completing C1, and low rates of dose reduction (9%) or discontinuation (8%) due to treatment-related AEs. CRS, a known effect of bispecific antibodies, was predominantly confined to the step-up dosing period (eight patients experienced CRS after 0.7/4/20/80 mg step-up dosing) and was generally manageable with supportive care. With 0.7/4/20 mg step-up dosing, one patient experienced a grade 3 CRS event and one had a grade 2 ICANS event. Monitoring in an inpatient hospital setting was required up to and including the first full weekly dose in ELM-2, although based on the observed safety profile, ongoing phase III studies of odronextamab are enrolling in an outpatient setting. This is an important consideration for reducing health care inequities and gaps in care for patients with R/R lymphoma who may not have access to inpatient facilities or CAR-T centers.

Infections were reported in most patients, which may be expected in this patient setting due to preexisting immunosuppression from the underlying malignancy, exposure to prior cytotoxic therapies,[29-31] and the expected mechanism of action of odronextamab to deplete B cells. Rapid, sustained B-cell depletion has been reported in the ELM-1 and ELM-2 studies,[32] with evaluation of B-cell recovery a focus of future studies. CD3+, CD4+, and CD8+ T-cell counts were maintained following odronextamab treatment. The

https://doi.org/10.1016/j.annonc.2024.08.2239

most common infection was COVID-19 (any grade, 37%), and COVID-19 was the infection that led to the most deaths. This may be attributed in part to ELM-2 enrollment starting early in the COVID-19 pandemic, when no vaccines were available and mortality was high, and continuing when vaccines were available but transmissible variants were common and social distancing measures were easing.

In conclusion, this study has demonstrated the compelling, durable efficacy and generally manageable safety of odronextamab in R/R FL. These results support further investigation of odronextamab in FL, as monotherapy and in combination with other agents. Phase III trials of odronextamab in the earlier-line setting are ongoing.[33-35]

ACKNOWLEDGEMENTS

The authors thank the patients, their families, the ELM-2 study team, all other investigators, and all investigational site members involved in this study, especially during the challenging times of the COVID-19 pandemic. Medical writing support was provided by Neil Harrison and Georgina Bartle of Oberon, OPEN Health Communications, and was funded by Regeneron Pharmaceuticals, Inc., in accordance with Good Publication Practice (GPP) guidelines.

FUNDING

This work was supported by Regeneron Pharmaceuticals, Inc. (no grant number).

DISCLOSURE

TMK reports honoraria from Amgen, AstraZeneca/MedImmune, IMBDx, Inc., Janssen, and Takeda; has provided consultancy for AstraZeneca/MedImmune, Boryung, F. Hoffmann-La Roche, Janssen, Novartis, Regeneron Pharmaceuticals, Inc., Roche, Samsung Bioepis, Takeda, and Yuhan; speaker bureau fees for IMBDx, Inc., Janssen, and Takeda; membership on advisory committees for BeiGene, Janssen, Novartis, Regeneron Pharmaceuticals, Inc., Roche, and Takeda; and an uncompensated relationship with AstraZeneca/MedImmune, Boryung, Novartis, and Roche. MTas reports consultancy for Roche and Takeda. SN reports consultancy for Mundipharma and research funding from Novartis. SGC holds stock or stock options for LucasBio and ViGenCell. JCV reports consultancy and/or an advisory role for Kite/Gilead, Regeneron Pharmaceuticals, Inc., Curio Science, and TG Therapeutics; and research funding from Regeneron Pharmaceuticals, Inc., Aptose Biosciences, Epizyme, Enterome, and Genentech. MM reports consultancy for Regeneron Pharmaceuticals, Inc. BT reports honoraria from AbbVie, Gilead, Incyte, and Kite. DT reports consultancy and/or an advisory role for Regeneron Pharmaceuticals, Inc., AbbVie, BeiGene, Immunovant, and Gilead; and travel/accommodation/other expenses from BeiGene. JW reports consultancy for AbbVie, Gilead, Novartis, Roche, Takeda, and MSD; research or clinical trial funding from GSK, Novartis, and Roche; and honoraria from AbbVie, Amgen, Gilead, GSK, Novartis, Roche, and Takeda. GC reports consultancy for Bristol Myers Squibb (BMS), Takeda, and Regeneron Pharmaceuticals, Inc.; and research funding from BMS, Regeneron Pharmaceuticals, Inc., Hutchmed, Bayer, Incyte, Pharmacyclics, Merck, AstraZeneca, Roche, Dizal Pharma, Pfizer, Innate Pharma, and Amgen. EB reports research or clinical trial funding from Amgen and BMS; honoraria from Kite/Gilead, Incyte, Novartis, Pfizer, Roche, BMS, and Takeda; consultancy for Roche; and other (personal) fees from Kite/Gilead, BMS, Novartis, and Pfizer. SG reports honoraria from Kite/Gilead. DJ reports research funding from Atara Biotherapeutics, AstraZeneca, Debiopharm, Loxo Oncology, MEI Pharma, Regeneron Pharmaceuticals Inc., Seagen, Trillium Therapeutics; and membership of advisory committees of Affimed and Daiichi Sankyo. EIJ reports consultancy for AbbVie and AstraZeneca; and honoraria from AbbVie, AstraZeneca, Janssen, and Novartis. MTan reports membership of advisory committees for AbbVie, Janssen, and Incyte. BS, AU, MZ, SS, JBV, AC, HM, and SA hold stock or stock options for and are employees of Regeneron Pharmaceuticals, Inc. SL reports consultancy for AstraZeneca, BeiGene, BMS, Incyte, Janssen, Kite, Regeneron Pharmaceuticals, Inc., Roche, Sobi, and Takeda. All other authors have declared no conflicts of interest.

DATA SHARING

Patient personal data will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to these data by any unauthorized third party. 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 manuscript. Individual anonymized participant data will be considered for sharing: (i) once the product and indication have been approved by major health authorities [e.g. Food and Drug Administration (FDA), European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency (PMDA), etc.] or development of the product has been discontinued globally for all indications on or after April 2020 and there are no plans for future development; (ii) if there is legal authority to share the data; and (iii) there is not a reasonable likelihood of participant re-identification. Requests should be submitted to https://vivli.org/.

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