Linvoseltamab for Treatment of Relapsed/Refractory Multiple Myeloma

Naresh Bumma, MD[1]; Joshua Richter, MD[2]; Sundar Jagannath, MD[2]; Hans C. Lee, MD[3]; James E. Hoffman, MD[4]; Attaya Suvannasankha, MD[5]; Jeffrey A. Zonder, MD[6]; Mansi R. Shah, MD[7]; Suzanne Lentzsch, MD, PhD[8]; Rachid Baz, MD[9]; Joseph J. Maly, MD[10]; Swathi Namburi, MD[11]; Matthew J. Pianko, MD[12]; Jing Christine Ye, MD, MS[12]; Ka Lung Wu, MD, PhD[13]; Rebecca Silbermann, MD[14]; Chang-Ki Min, MD[15]; Marie-Christiane Vekemans, MD[16]; Markus Munder, MD[17]; Ja Min Byun, MD[18]; Joaquín Martínez-Lopez, MD[19]; Kaniel Cassady, PhD[20]; Michelle DeVeaux, PhD[20]; Dhruti Chokshi, BS[20]; Anita Boyapati, PhD[20]; Anasuya Hazra, PhD[20]; George D. Yancopoulos, MD, PhD[20]; L. Andres Sirulnik, MD, PhD[20]; Karen Rodriguez Lorenc, MD[20]; Glenn S. Kroog, MD[20]; Yariv Houvras, MD, PhD[20]; and Madhav V. Dhodapkar, MD[21]

DOI https://doi.org/10.1200/JCO.24.01008

ABSTRACT

PURPOSE We present a phase I/II first-in-human trial evaluating the safety and efficacy of 50 mg and 200 mg doses of linvoseltamab, a B-cell maturation antigen × CD3 bispecific antibody in relapsed/refractory multiple myeloma (RRMM).

METHODS Phase II eligible patients had RRMM that either progressed on/after ≥three lines of therapy including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody or was triple-class (PI/IMiD/anti-CD38) refractory. Phase II treatment was once a week through week 14 and then once every 2 weeks. Phase II 200 mg patients who achieved a ≥very good partial response by week 24 received linvoseltamab once every 4 weeks. The primary end point in phase II was overall response rate (ORR).

RESULTS Among the 117 patients treated with 200 mg, the median age was 70 years, 39% had high-risk cytogenetics, and 28% had penta-refractory disease. At a median follow-up of 14.3 months, the ORR was 71%, with 50% achieving ≥complete response (CR). In 104 patients treated with 50 mg at a median follow-up of 7.4 months, the ORR was 48%, with 21% achieving ≥CR. The median duration of response (DOR) for 200 mg patients (n = 83) was 29.4 months (95% CI, 19.2 to not evaluable). Among 200 mg patients, the most common adverse events included cytokine release syndrome (35.0% Gr1, 10.3% Gr2, 0.9% Gr3), neutropenia (0.9% Gr2, 18.8% Gr3, 23.1% Gr4), and anemia (3.4% Gr1, 4.3% Gr2, 30.8% Gr3). Immune effector cell-associated neurotoxicity syndrome occurred in 7.7% of patients (2.6% each Gr1, Gr2, Gr3). Infections were reported in 74.4% of patients (33.3% Gr3, 2.6% Gr4); infection frequency and severity declined over time.

CONCLUSION Linvoseltamab 200 mg induced deep and durable responses, with a median DOR of 29.4 months, in patients with RRMM with an acceptable safety profile.

ACCOMPANYING CONTENT

Appendix
Data Sharing Statement
Data Supplement
Protocol

Accepted May 17, 2024
Published June 16, 2024

J Clin Oncol 42:2702-2712

INTRODUCTION

Multiple myeloma (MM) remains an incurable hematologic malignancy despite advances in antimyeloma therapies. With repeated cycles of relapse and remission, patients with myeloma experience increasingly shorter periods of remission and their disease often becomes refractory to the three principal antimyeloma drug classes: proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 antibodies.[1,2] Therapies utilizing different mechanisms of action that are well tolerated and induce deep and durable remission are needed.[1,3]

B-cell maturation antigen (BCMA; also known as TNFRSF17) expression is restricted to plasmablasts and plasma cells[4-6] and has emerged as an important drug target for both chimeric antigen receptor T-cell (CAR-T) therapies and bispecific antibodies in the treatment of MM.[7-11] In heavily treated patients with relapsed/refractory MM (RRMM), approved BCMA-targeted CAR-T therapies have shown overall response rates (ORRs) of 73%-97%,[8,12] whereas bispecific BCMA × CD3 (BCMA×CD3) antibodies have shown ORRs of 61%-63%.[10,11,13] CAR-T therapies are complicated by manufacturing and access challenges and usually require bridging therapy, which may lead to delays

CONTEXT

Key Objective

Does linvoseltamab, a B-cell maturation antigen × CD3 antibody, confer clinical benefit for patients with relapsed refractory multiple myeloma who have progressed on or after three prior lines of therapy or who are triple-refractory (to a(n) proteasome inhibitor, immunomodulatory drug, and anti-CD38 monoclonal antibody)?

Knowledge Generated

Linvoseltamab (200 mg) induced 71% overall response rate with 50% rate of complete response (CR) or better (≥CR), and a median duration of response of 29.4 months. The most common adverse event was cytokine release syndrome in 46% of patients (35.0% grade 1, 10.3% grade 2, 0.9% grade 3). A response-adapted regimen enabled patients with very good partial response or better to shift to once every 4-week dosing after 24 weeks on study; this regimen was associated with both sustained efficacy and a decrease in infection rate over time.

Relevance *(J.W. Friedberg)*

Linoseltamab represents another bispecific antibody treatment option for patients with relapsed/refractory myeloma. Future trials should evaluate this agent earlier in the disease course, and optimal sequences of this agent with other therapies, including chimeric antigen receptor T-cell approaches.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

in treatment and disease progression.[8] CAR-T treatments are associated with risk of rare but serious adverse events (AEs), including Parkinsonism and secondary malignancies.[14-16] By contrast, BCMA×CD3 bispecific antibodies are off-the-shelf medicines that can be administered promptly in patients without the need for bridging therapy. Notable side effects with current US Food and Drug Administration (FDA)–approved BCMA×CD3 bispecific antibodies (teclistamab, elranatamab) include cytokine release syndrome (CRS), neurotoxicity including immune effector cell-associated neurotoxicity syndrome (ICANS), and infections.[10,11,17,18]

Linvoseltamab (REGN5458) is a fully human BCMA×CD3 bispecific antibody created using the Veloci-Bi platform.[19,20] Linvoseltamab was designed to have minimal immunogenicity and favorable molecular stability and pharmacokinetic (PK) properties.[19,20] In preclinical studies, linvoseltamab showed promising antitumor activity.[21] LINKER-MM1 is a phase I/II first-in-human study of linvoseltamab monotherapy in 282 patients with triple-class RRMM. In the phase I portion of the study, 73 patients were treated across nine dose levels with full doses ranging from 3 mg to 800 mg. In accordance with FDA's Project Optimus,[22] to identify the optimal full dose for treatment of RRMM, two phase II cohorts were enrolled, a cohort testing a full dose of 50 mg (n = 104), and a second cohort testing a full dose of 200 mg (n = 105). Here we present the efficacy, safety, and clinical pharmacology data from the phase I and phase II portions of LINKER-MM1, with a focus on patients treated with a 200 mg full dose.

METHODS

Participants

Eligible patients had active MM, measurable serum or urine markers as defined by the International Myeloma Working Group (IMWG),[23] and exposure to three or more prior lines of therapy including an IMiD, a PI, and an anti-CD38 antibody. Alternatively, phase I patients were required to have double-class refractory disease (refractory to both an IMiD and a PI); phase II patients were required to have triple-class refractory disease (refractory to an IMiD, a PI, and an anti-CD38 antibody). In addition, patients had to be age ≥18 years and have an Eastern Cooperative Oncology Group performance status of 0 or 1. Key exclusion criteria included primary systemic light-chain amyloidosis, known CNS involvement by MM, a history of neurodegenerative condition, a CNS movement disorder, or prior treatment with BCMA-directed immunotherapies excluding BCMA antibody-drug conjugate (for complete inclusion/exclusion criteria see the online protocol). All patients provided written informed consent before enrollment.

Study Design and Oversight

LINKER-MM1 is an open-label, first-in-human, phase I/II clinical trial (ClinicalTrials.gov identifier: NCT03761108) conducted at 23 centers worldwide: the United States (14), South Korea (3), Belgium (2), Germany (2), and Spain (2). The phase I dose escalation portion followed a modified 3 + 3 (4 + 3) dose-escalation design with a 28-day dose-limiting toxicity observation period. Procedures and objectives for

the phase I portion are provided in the Data Supplement (Table S1, pages 4-7, online only).[22,24] The phase II portion tested two full doses: 50 mg and 200 mg.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study protocol and all amendments were approved by the institutional review board or independent ethics committee at each participating site and are available online. All authors reviewed the data for accuracy and collaborated in the preparation of the manuscript.

Procedure

To minimize the incidence and severity of CRS, beginning in phase I dose level 6 and continuing thereafter, a 5 mg (day 1)/25 mg (day 8) step-up regimen was used before the first full dose (day 15). In phase II, a full dose of linvoseltamab intravenous (IV) (50 mg or 200 mg) was administered once a week from week 3 through week 14, after which patients transitioned to administration once every 2 weeks starting on week 16. In phase II, patients treated at a full dose of 200 mg transitioned to once every 4 weeks dosing if they achieved a very good partial response (VGPR) or better and had a minimum of 24 weeks on treatment. Treatment in phase II was continued until progressive disease (PD) or other discontinuation criteria were met (eg, withdrawal of consent, or physician decision). Intrapatient dose escalation to 200 mg was permitted for phase II 50 mg patients who progressed after 4-14 weeks on treatment. Enrollment in phase II cohorts was staggered and partially overlapped. When enrollment in phase II cohorts overlapped, alternating assignment of the full dose was made by an interactive response technology system.

During step-up dosing and the first full dose, infusions were administered over 4 hours. If subsequent infusions were adequately tolerated, infusion time was reduced to 30 minutes as early as week 5. Premedication with dexamethasone, antihistamines, acetaminophen, and/or nonsteroidal anti-inflammatory drugs was required for all patients before each of the step-up doses and before the first full dose. The requirement for hospitalization was reduced during the study, and the final protocol requirement was hospitalization for 24 hours after the first two step-up doses. Safety evaluations were conducted at each dosing visit. AEs severity was graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, except for CRS which was graded per the American Society for Transplantation and Cellular Therapy grading system.[25] Cases of ICANS were adjudicated by the sponsor on the basis of signs and symptoms of ICANS consistent with published guidelines.[25]

After the end of treatment, patients were evaluated in a safety follow-up period comprising visits at day 30, week 8, and week 12. Thereafter, patients who discontinued treatment because of a reason other than PD entered an efficacy follow-up period comprising visits every 8 weeks until PD or initiation of a new antimyeloma therapy. After the safety and efficacy follow-up periods, patients were followed for survival.

Outcomes

The primary objective in phase II was to assess the ORR of linvoseltamab as determined by an independent review committee (IRC) per IMWG criteria.[26] Secondary objectives included assessment of duration of response (DOR) and progression-free survival (PFS) as determined by an IRC and the investigator, investigator-assessed ORR, rate of minimal residual disease (MRD; negative threshold of 10^{-5}; Data Supplement, page 6-7), overall survival (OS), PK (Data Supplement, page 6-7) properties, evaluation of linvoseltamab safety and tolerability, and characterization of linvoseltamab immunogenicity (Data Supplement, page 7). Exploratory objectives included evaluation of serum soluble BCMA (sBCMA; Data Supplement, pages 5-6) concentrations at baseline and over time.

Statistical Analysis

For phase II, to provide at least 80% power to reject the null hypothesis of a ≤31% ORR, a sample size of 104 patients was calculated to be required for each of the phase II cohorts on the basis of an exact test, using a one-sided significance level of 0.025 if the true ORR is 45%. Categorical and continuous data were summarized with frequencies and percentages or descriptive statistics, respectively. The Clopper-Pearson exact CI test was used to generate 95% CIs for ORR. DOR, PFS, and OS were estimated using Kaplan-Meier (KM) analysis. Duration of follow-up was estimated using reverse KM analysis. The data cutoff was January 6, 2024, for the safety and efficacy data analyses.

RESULTS

Patients

Between January 23, 2019, and October 18, 2022, 282 patients with RRMM were enrolled and treated with linvoseltamab (Data Supplement, Fig S1). Phase I results are provided in the Data Supplement (pages 9-13, Fig S2 and Tables S2-S4). An analysis of phase I data led to the identification of two full doses for study in phase II: 50 mg and 200 mg. A total of 117 patients were treated at a full dose of 200 mg (105 patients in phase II, 12 patients in phase I), and 104 patients were treated at a full dose of 50 mg. For immunogenicity and phase II PK and sBCMA data see the Data Supplement (pages 13-15, Figs S3 and S4). As of January 6, 2024, treatment was ongoing in 41 (35%) and 11 (11%) patients receiving 200 mg or 50 mg, respectively. The median treatment duration on 200 mg was 53.0 weeks and on 50 mg was 13.9 weeks.

Baseline characteristics of patients treated at a full dose of 50 mg and 200 mg were broadly similar with few

TABLE 1. Baseline Patient and Disease Characteristics

Patient and Disease Characteristic	50 mg (n = 104)	200 mg (n = 117)
Age		
Years, median (range)	65 (45-90)	70 (37-91)
≥75 years, No. (%)	17 (16.3)	31 (26.5)
Male, No. (%)	56 (53.8)	64 (54.7)
Race, No. (%)		
White	75 (72.1)	83 (70.9)
Black or African American	14 (13.5)	20 (17.1)
Asian	6 (5.8)	10 (8.5)
ECOG performance status, No. (%)		
0	36 (34.6)	32 (27.4)
1	67 (64.4)	85 (72.6)
2	1 (1.0)	0
ISS stage, No. (%)		
I	43 (41.3)	49 (41.9)
II	35 (33.7)	41 (35.0)
III	24 (23.1)	21 (17.9)
Missing	2 (1.9)	6 (5.1)
Extramedullary plasmacytomas per IRC, No. (%)	17 (16.3)	19 (16.2)
High-risk cytogenetics,[a] No. (%)	28 (26.9)	46 (39.3)
BMPC percentage, No. (%)		
<50%	41 (39.4)	65 (55.6)
≥50%	37 (35.6)	28 (23.9)
Missing	21 (20.2)	22 (18.8)
Soluble BCMA, ng/mL, median (range)	379.0 (26.1-10,020.0)	368.0 (18.7-4,430.0)
Prior autologous transplant, No. (%)	83 (79.8)	77 (65.8)
No. of prior lines, median (range)	6 (3-14)	5 (2-16)
Exposure status, No. (%)		
At least triple-exposed	104 (100.0)	117 (100.0)
At least quad-exposed	104 (100.0)	112 (95.7)
At least penta-exposed	95 (91.3)	90 (76.9)
Refractory status, No. (%)		
At least triple-refractory	97 (93.3)	96 (82.1)
At least quad-refractory	86 (82.7)	77 (65.8)
At least penta-refractory	56 (53.8)	33 (28.2)
Refractory to last line of therapy,[b] No. (%)	93 (89.4)	100 (85.5)

NOTE. Triple-exposed/refractory: ≥one PI, ≥one IMiD, and ≥one anti-CD38 antibody. Quad-exposed/refractory: ≥two PI, ≥one IMiD, and ≥one anti-CD38 antibody or ≥one PI, ≥two IMiD, and ≥one anti-CD38 antibody. Penta-exposed/refractory: ≥two PI, ≥two IMiD, and ≥one anti-CD38 antibody. Patients treated with 200 mg had higher percentage of age ≥75 years and of high-risk cytogenetics; 50 mg-treated patients had higher percentages of bone marrow plasma cells ≥50%, prior autologous stem cell transplant, and triple/quad/penta refractory status.

Abbreviations: BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cells; CD, cluster of differentiation; ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; IRC, independent review committee; ISS, International Staging System; PI, proteasome inhibitor.

[a]Presence of del(17p) and/or translocation t(4;14) or translocation t(14;16).

[b]Includes patients with a lack of response or relapse within 60 days of last line of therapy.

exceptions (Table 1). Among 200 mg patients, the median age was 70 (range, 37-91) years, the median number of prior lines of therapy was five (range, 2-16), and 77% of patients were penta-exposed (exposed to two IMiDs, two PIs, and an anti-CD38 antibody). Extramedullary disease, defined as non–bone-associated plasmacytoma ≥2 cm, was present in 16% of patients, and 28% had penta-refractory disease. High-risk cytogenetics was present in 39% of patients while 35% and 18% of patients had International Staging System (ISS) stage II-III disease, respectively. Seventeen percent of patients were Black or African American.

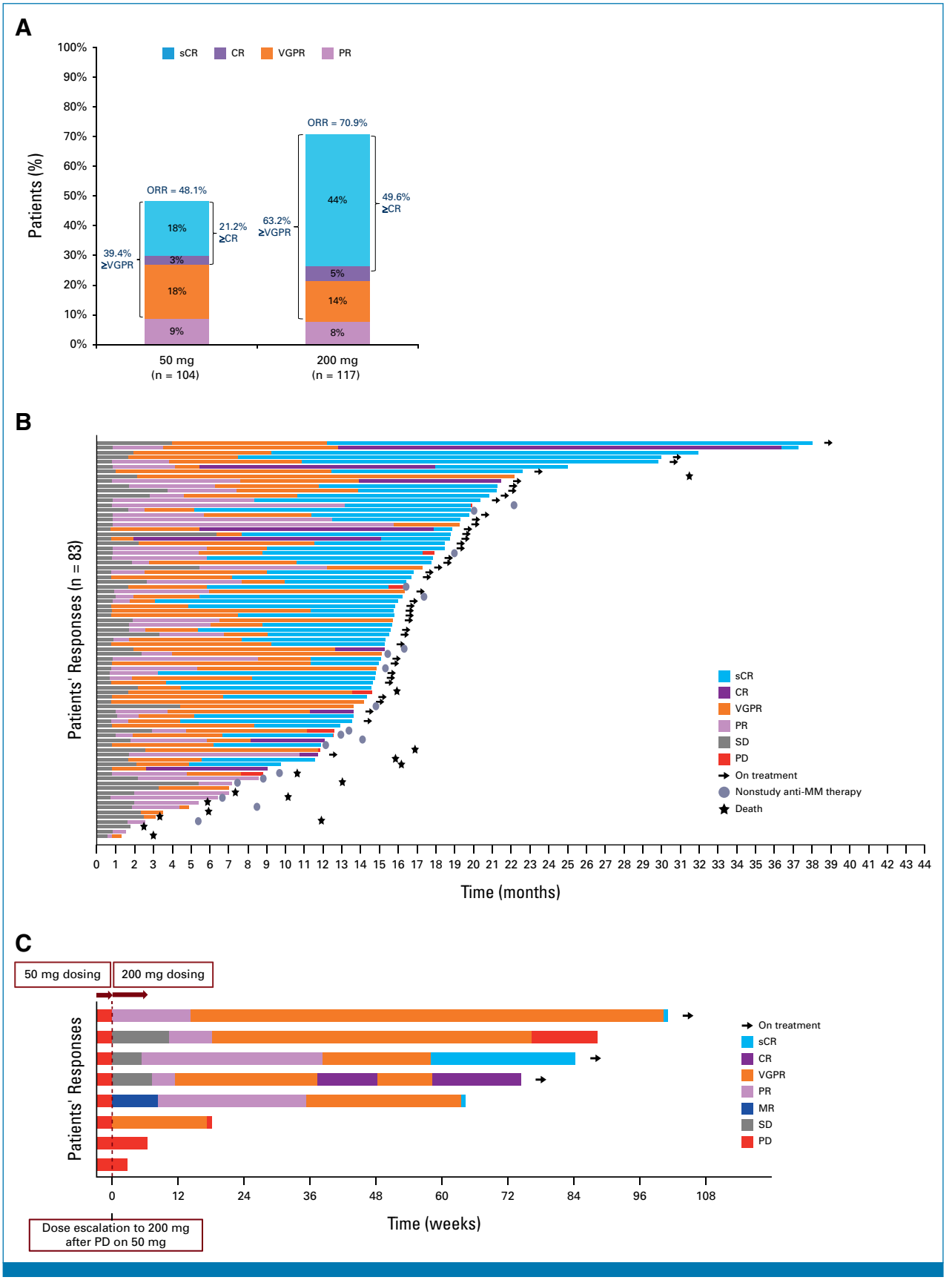

FIG 1. Overall response to linvoseltamab in relapsed/refractory multiple myeloma. (A) The best overall response per IRC per IMWG criteria[26] in patients treated at a full dose of 50 mg (n = 104 patients from phase II) or 200 mg (n = 105 phase II patients combined with n = 12 phase I patients, total N = 117 patients). The data cutoff for response assessment was (continued on following page)

FIG 1. (Continued). January 6, 2024. (B) The evolution of responses over time among 83 patients who achieved a PR or better treated at 200 mg. (C) The evolution of responses over time among eight patients who underwent intrapatient dose escalation from 50 mg to 200 mg. Patients assigned to 50 mg dose in phase II were permitted to dose escalate to 200 mg if disease progression occurred between 4 and 12 weeks of treatment. Assessment of disease progression and response were determined by the investigator. CR, complete response; IMWG, International Myeloma Working Group; IRC, independent review committee; MR, minimal response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good partial response.

Efficacy

The median duration of follow-up was 14.3 months (range, 0.2-38.4) for 200 mg patients and 7.4 months (range, 0.4-42.0) for 50 mg patients. Patients treated with 200 mg linvoseltamab had an ORR of 70.9%, with 63.2% of patients achieving ≥VGPR and 49.6% achieving ≥complete response (CR). Patients treated with 50 mg linvoseltamab had an ORR of 48.1%, with 39.4% of patients achieving ≥VGPR and 21.2% of patients achieving ≥CR (Fig 1A; Data Supplement, Table S5). Both phase II cohorts (50 mg and 200 mg), therefore, met the prespecified criteria to reject the null hypothesis. Among 200 mg patients in ≥CR (n = 58) and MRD evaluable by clonoSEQ (n = 21), the MRD-negative (threshold 10^{-5}) rate was 90.5% (19/21). MRD-negative status by either EuroFlow (n = 7) or clonoSEQ was 92.9% (26/28). A total of eight patients who progressed on 50 mg underwent intrapatient dose-escalation to 200 mg. Six of these eight patients (75%) had a response with 200 mg linvoseltamab, all achieving a VGPR (Fig 1C).

In patients who received the full dose of 200 mg responses occurred early, were durable, and deepened over time. The median time to response (≥PR) was 1 month (range, 0.5-6.3), the median time to ≥VGPR was 2.6 months (range, 0.7-15.7), and the median time to ≥CR was 8.5 months (range, 1.6-14.1; Fig 1B). The KM estimated median DOR was 29.4 months (95% CI, 19.2 to not evaluable [NE]), and the probability of maintaining a response at 12 months was 80.9% (95% CI, 70.3 to 88.0; Fig 2A). The KM-estimated median PFS was not reached (NR; 17.3 months to NE; Fig 2B), with the probability of being progression free at 12 months of 70.0% (95% CI, 60.1 to 78.0; Fig 2B). The KM-estimated median OS was 31.4 months (21.6 to NE; Fig 2C), and the probability of survival at 12 months was 75.3% (95% CI, 66.0 to 82.3; for 50 mg; Data Supplement, Figs S5 and S6 and Table S5).

An analysis of overall response to 200 mg in prespecified subgroups demonstrated high efficacy across high-risk and high disease burden populations. ORR was 71.0% among patients age ≥75 years, 67.4% in patients with high-risk cytogenetics, 61.9% in patients with ISS stage III disease, 66.7% in patients with penta-refractory disease, and 52.6% in patients with extramedullary plasmacytomas ≥2 cm (Fig 3; Data Supplement, Fig S7). Patients with prior exposure to the anti-BCMA antibody-drug conjugate belantamab mafodotin (n = 10) achieved a 70% ORR. ORR was also high in Black or African American patients (85.0%).

Of the 61 of 105 (58.1%) phase II 200 mg patients who had ≥24 weeks of study drug exposure, 58 of 61 (95.1%) patients achieved an investigator-assessed response of ≥VGPR and switched to once every 4-week therapy. KM-estimated median DOR was NR (95% CI, 19.2 months to NE), and the probability of being progression-free at 12 months was 89.3% (95% CI, 77.7 to 95.0). Of 31 patients who transitioned to once every 4-week dosing before achieving a CR or better, 20 (64.5%) had a deepening of response to ≥CR (Data Supplement).

Safety

All patients treated at a full dose of 50 mg or 200 mg received at least one dose of linvoseltamab and were included in the safety analyses (Table 2; Data Supplement, Tables S6-S9). Overall rates of treatment-emergent adverse events (TEAEs) were similar between 50 mg and 200 mg except for neutropenia which was higher in patients treated at 200 mg (42.7% overall, 41.9% grade 3-4) compared with 50 mg (28.8% overall, 26.9% grade 3-4). All patients treated at 200 mg experienced TEAEs, with 73.5% of patients experiencing grade 3-4 events. Discontinuation because of TEAEs occurred in 18.8% of patients treated at 200 mg including 7.7% that were deemed related to linvoseltamab. The majority of TEAEs leading to discontinuation were due to infections (9.4%); 75 of 117 (64.1%) of patients received intravenous immune globulin. TEAEs that led to death within 30 days of the last treatment dose were reported in six (5.1%) patients treated at 200 mg, five of which were due to infection. In 200 mg treated patients, deaths have occurred in 35 of 117 (30%) patients while on study. There were three treatment-related deaths due to infections: *pneumocystis jirovecii* pneumonia (PJP), progressive multifocal leukoencephalopathy, and pseudomonal sepsis.

CRS occurred in 46% of patients treated at 200 mg, grade 1 in 35% of patients, grade 2 in 10% of patients, one case (1%) of grade 3, and no cases of grade ≥4 (Data Supplement, Fig S8). Most CRS occurred in the step-up dosing period, including the grade 3 CRS event. The median time to CRS onset was 11 hours (measured from end of infusion; range, −1.1 to 183.6), and the median time to resolution of CRS was 15.6 hours (range, 1.0-96.0; Data Supplement, Table S10).

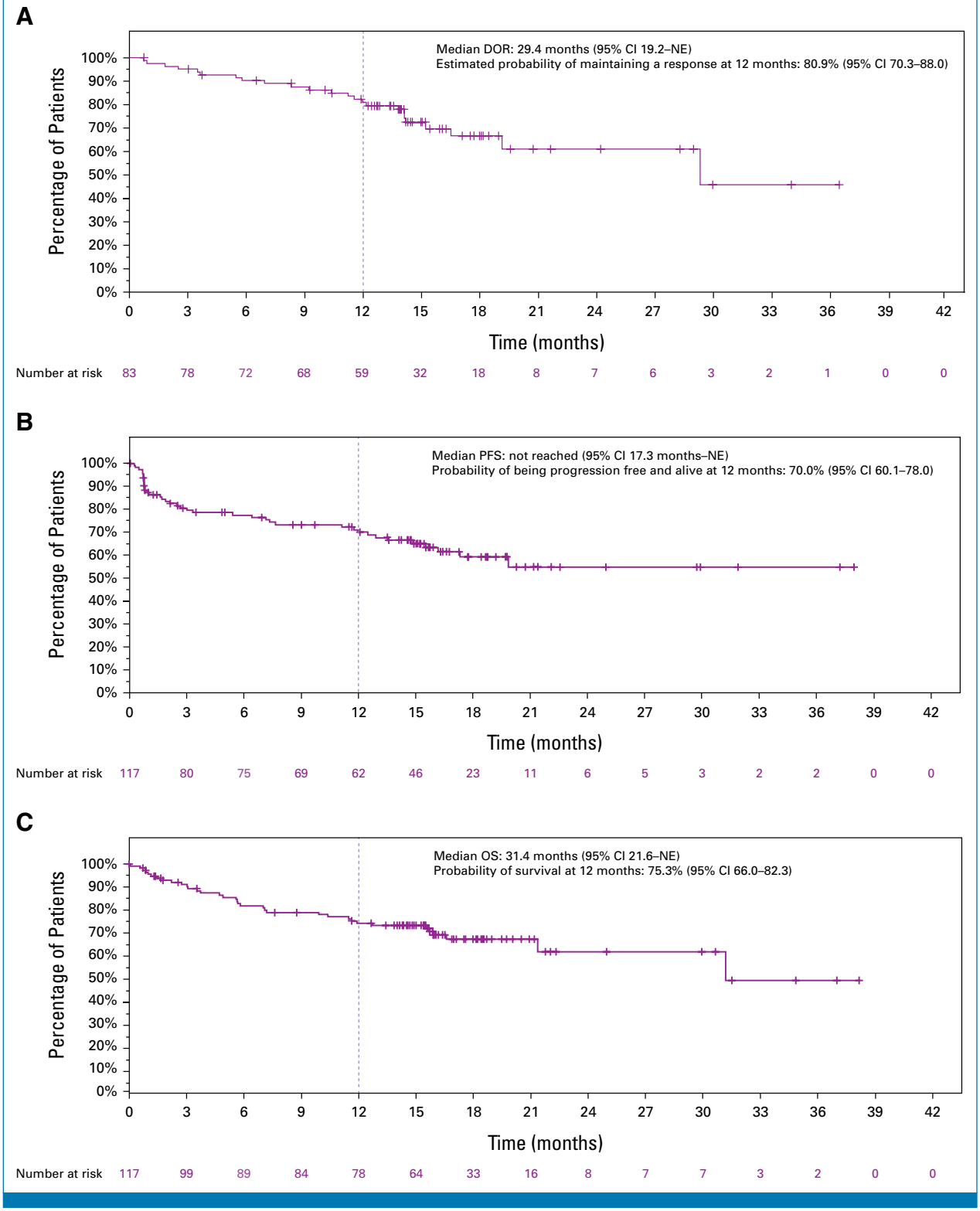

FIG 2. KM analysis of DOR, PFS, and OS. (A) DOR to linvoseltamab among patients who had a PR or better at a full dose of 200 mg. (B) PFS in all patients treated at a full dose of 200 mg. Response assessment and progression was determined by an IRC. (C) OS in all patients treated at a full dose of 200 mg. Tick marks on the curve indicate censored data. DOR, duration of response; IRC, independent review committee; KM, Kaplan-Meier; NE, nonevaluable; OS, overall survival; PFS, progression-free survival; PR, partial response.

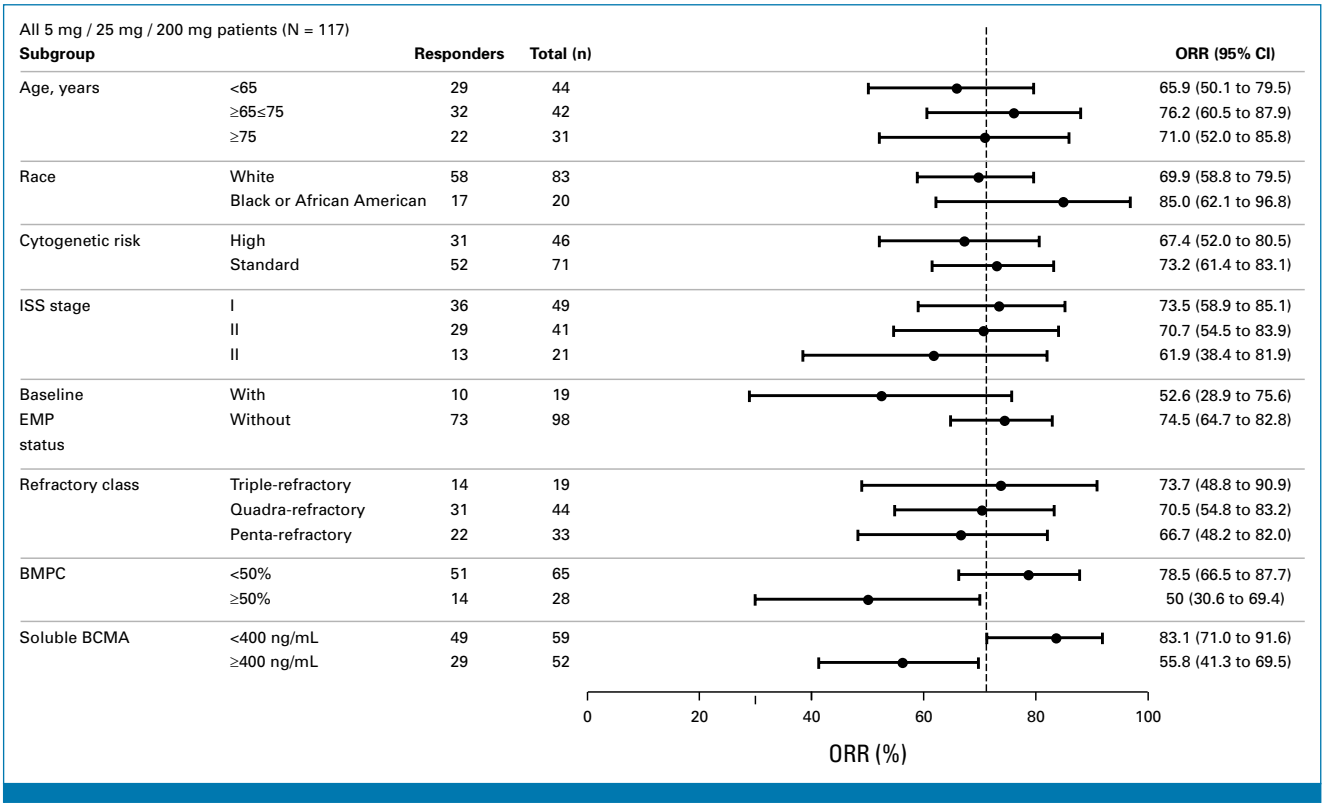

FIG 3. Forest plot illustrating the response rate in prespecified subgroups among 200 mg treated patients. A solid circle denotes the response rate, as determined by the IRC in prespecified subgroups, and whiskers indicate the 95% CI. A vertical dashed line denotes the ORR. High-risk cytogenetics, presence of del(17p) and/or t(4;14) or t(14;16). BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cells; EMP, extramedullary plasmacytoma; IRC, independent review committee; ISS, International Staging System; ORR, overall response rate.

Treatment of CRS with tocilizumab or corticosteroids was at investigator discretion and was reported in 22 (19%) and 13 (11%) patients, respectively (Data Supplement, Fig S9). ICANS occurred in nine (7.7%) patients (2.6% for each, grade 1, 2, and 3) treated in the 200 mg cohort. Most patients (8/9) experienced ICANS during step-up dosing, and symptoms of ICANS lasted a median of 2 days (range, 1-11 days) and resolved completely (one patient withdrew consent and no additional information was available). All ICANS events were concurrent with CRS or infusion-related reactions (IRRs).

Infections occurred in 74.4% of patients treated with the 200 mg dose, with 33.3% grade 3 and 2.6% grade 4. Opportunistic infections, including CMV reactivation or infection, occurred in 10.3% of patients treated with 200 mg, with 6.0% grade 3-4. The most frequent opportunistic infection was PJP (4%). After instituting PJP prophylaxis, there were no additional cases of PJP. The frequency and severity of infections decreased over time. In the 200 mg cohort, the rate of grade 3-4 infections was 20%-22% between 0 and 6 months, and 4%-8% between 6 and 15 months (Data Supplement, Table S11). Notably, among patients who developed a response of ≥CR, the rate of grade 3-4 infections was 2%-7% between 6 and 15 months, and there were no deaths due to infection. We also observed an increase in hemoglobin in responders over time (Data Supplement, Fig S10).

DISCUSSION

In this phase I/II clinical trial, a full dose of 200 mg IV linvoseltamab led to deep and durable responses in patients with RRMM. On the basis of the totality of the safety and efficacy data in this clinical trial comparing 50 mg and 200 mg dosing, including results from patients who underwent intrapatient dose-escalation, 200 mg was selected as the optimal dose of linvoseltamab. A rigorous approach to dose optimization including intrapatient dose escalation and exploration of safety and efficacy in two parallel phase II cohorts (which is consistent with the guidelines of FDA's Project Optimus[22]) reinforces the strength and validity of these data.

At a median duration of 14.3 months follow-up, treatment with the full dose of 200 mg was associated with an ORR of 70.9%, ≥VGPR rate of 63.2%, and ≥CR rate of 49.6%. Responses occurred rapidly (with median time to response of 1 month) and were durable (with the probability of maintaining a response at 12 months of 80.9%, and the probability of being progression free at 12 months of 70.0%). The LINKER-MM1 200 mg patient population is representative of patients with late-line RRMM: 27% of patients age ≥75 years, 35% and 18% ISS stage II-III disease, 16% with extramedullary plasmacytoma at baseline, 39% with high-risk cytogenetics, 28% with penta-refractory disease,

TABLE 2. TEAEs in ≥20% of Patients

Treatment exposure and TEAEs	50 mg (n = 104)		200 mg (n = 117)	
Treatment exposure, weeks, median (range)	13.9 (2.0-160.0)		53.0 (1.0-167.0)	
TEAEs[a]	Any Grade, No. (%)	Grade 3-4, No. (%)	Any Grade, No. (%)	Grade 3-4, No. (%)
No. of patients with TEAE	102 (98.1)	75 (72.1)	117 (100)	86 (73.5)
Hematologic TEAEs				
Neutropenia[b]	30 (28.8)	28 (26.9)	50 (42.7)	49 (41.9)
Anemia[b]	44 (42.3)	39 (37.5)	45 (38.5)	36 (30.8)
Nonhematologic TEAEs				
Cytokine release syndrome	57 (54.8)	2 (1.9)	54 (46.2)	1 (0.9)
Cough	36 (34.6)	0	43 (36.8)	0
Diarrhea	32 (30.8)	3 (2.9)	44 (37.6)	2 (1.7)
Fatigue	31 (29.8)	0	39 (33.3)	0
Arthralgia	34 (32.7)	3 (2.9)	35 (29.9)	0
Hypokalemia[b]	17 (16.3)	4 (3.8)	29 (24.8)	4 (3.4)
Nausea	28 (26.9)	1 (1.0)	27 (23.1)	0
COVID-19[b]	24 (23.1)	7 (6.7)	26 (22.2)	11 (9.4)
Headache[b]	31 (29.8)	0	27 (23.1)	1 (0.9)
Back pain	24 (23.1)	5 (4.8)	24 (20.5)	3 (2.6)
Pain in extremity	22 (21.2)	3 (2.9)	14 (12.0)	1 (0.9)
Dyspnea	21 (20.2)	3 (2.9)	24 (20.5)	1 (0.9)
Constipation	21 (20.2)	0	20 (17.1)	0

Abbreviation: TEAE, treatment-emergent adverse event.
[a]On linvoseltamab or within 30 days after last dose.
[b]Composite terms.

and 17% Black or African American patients. Linvoseltamab was found to be highly efficacious in all these prespecified subgroups. We also note that median baseline sBCMA was high (368.0 ng/mL [range, 18.7-4,430.0]) indicative of very high disease burden in study patients.

While cross-trial comparisons should be interpreted with caution, it is informative to contextualize linvoseltamab efficacy with other approved BCMA-targeted therapies. In comparison with BCMA-targeted CAR-T, ciltacabtagene autoleucel was associated with higher response rate (ORR 83%, ≥CR rate 67%, in patients who underwent leukapheresis).[8] However, at the 200 mg dose, linvoseltamab had higher ORR (70.9%) and ≥CR rate (49.6%) as compared with idecabtagene vicleucel (ORR 67%; ≥CR 30%, in patients who underwent leukapheresis).[12] In comparison with BCMA×CD3 bispecific antibodies, patients treated with the 200 mg dose of linvoseltamab experienced higher ORR (70.9%) and ≥CR (49.6%) rate than teclistamab (ORR 63%; ≥CR 39.4%)[10] and elranatamab (ORR 61%; ≥CR 35.0%).[11] Linvoseltamab induced responses in the majority of patients with ISS stage III disease (62% ORR *v* 35%—teclistamab[10]; 26.3%—Revised-ISS stage III, elranatamab[11]) or with extramedullary plasmacytoma at baseline (ORR 53% *v* 35.7%—teclistamab[10]; 38.5%—elranatamab [included paramedullary plasmacytomas]).

In patients with RRMM, linvoseltamab demonstrated a generally manageable safety profile that is generally comparable with that of other anti-BCMA bispecifics. Compared with teclistamab[10] and elranatamab,[11] patients treated with linvoseltamab had a shorter time to onset and to resolution of CRS and an overall lower rate of CRS. The median time to onset and the duration of CRS was 11 hours and 15 hours, respectively. CRS occurred in 46% of patients, with the majority being grade 1 (35% of patients) and a single case of grade 3 CRS. Finally, almost all CRS cases occurred during the first two doses of study drug. The unique CRS profile of linvoseltamab (shorter time to onset and resolution) has a meaningful clinical impact, allowing for a limited required duration of hospitalization or observation (24 hours on day 1 and 8) when compared with available anti-BCMA bispecifics and is likely related to the pharmacokinetics associated with IV administration and the use of a fully human antibody.[20] The overall rate of ICANS was 7.7% (grade 1-3, no grade ≥4 events occurred). Most patients experienced ICANS during step-up dosing (8/9 patients), and all cases occurred in the context of CRS or IRR.

The rate of grade 3-4 infections was 34%, and we observed a decline in this rate over time that appears most significant in patients achieving a deep response; notably, there were no deaths due to infection among patients treated at 200 mg who achieved a response of ≥CR. Similarly, responders

experienced a modest increase in hemoglobin levels, which may represent an improvement in bone marrow function. Opportunistic infections have emerged as an area of clinical concern in patients with MM especially those treated with bispecific antibodies. After instituting prophylaxis against PJP no additional cases were reported.

In summary, 200 mg linvoseltamab demonstrated high efficacy in patients with late-stage RRMM, including patients with high disease burden and high-risk features which is noteworthy in the context of other approved drugs in this class. A response-adapted regimen allowed patients treated at 200 mg who experience deep responses (≥VGPR) to shift to once every 4-week dosing after 24 weeks on study; this regimen maximized patient convenience, and was associated with both sustained efficacy, and a decrease in infection rate over time, particularly among patients with deep responses. These data suggest that linvoseltamab offers substantial clinical benefit for treatment of RRMM.

AFFILIATIONS

[1]The Ohio State University Comprehensive Cancer Center, Columbus, OH
[2]Icahn School of Medicine at Mount Sinai, New York, NY
[3]The University of Texas MD Anderson Cancer Centre, Houston, TX
[4]University of Miami Health System, Miami, FL
[5]Indiana University Simon Cancer Center and Roudebush VAMC, Indianapolis, IN
[6]Karmanos Cancer Institute, Detroit, MI
[7]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ
[8]Columbia University Medical Center, New York, NY
[9]Department of Malignant Hematology, H. Lee Moffitt Cancer Center, Tampa, FL
[10]Norton Cancer Institute, Louisville, KY
[11]Swedish Cancer Institute, Seattle, WA
[12]Rogel Cancer Center, University of Michigan Medical School, Ann Arbor, MI
[13]Ziekenhuis Netwerk Antwerpen Stuivenberg, Antwerp, Belgium
[14]Knight Cancer Institute, Oregon Health & Science University, Portland, OR
[15]Department of Hematology, College of Medicine, Catholic Hematology Hospital and Leukemia Research Institute, Seoul St Mary's Hospital, The Catholic University of Korea, Seoul, South Korea
[16]Department of Hematology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain (UCLouvain), Brussels, Belgium
[17]Department of Internal Medicine III, University Medical Center Mainz, Mainz, Germany
[18]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Korea
[19]Hospital 12 de Octubre, i+12, School of Medicine Universidad Complutense, CNIO, Madrid, Spain
[20]Regeneron Pharmaceuticals, Inc, Tarrytown, NY
[21]Emory University School of Medicine, Atlanta, GA

CORRESPONDING AUTHOR

Madhav V. Dhodapkar, MD; Twitter: @MadhavDhodapkar; e-mail: madhav.v.dhodapkar@emory.edu.

EQUAL CONTRIBUTION

N.B. and J.R. denotes co-primary authors.

CLINICAL TRIAL INFORMATION

NCT03761108

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.24.01008.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO.24.01008.

AUTHOR CONTRIBUTIONS

Conception and design: George D. Yancopoulos, L. Andres Sirulnik, Karen Rodriguez Lorenc, Glenn S. Kroog, Yariv Houvras, Anita Boyapati, Dhruti Chokshi
Provision of study materials or patients: Naresh Bumma, Joshua Richter, Sundar Jagannath, Hans C. Lee, James E. Hoffman, Attaya Suvannasankha, Jeffrey A. Zonder, Mansi R. Shah, Suzanne Lentzsch, Rachid Baz, Swathi Namburi, Matthew J. Pianko, Jing Christine Ye, Ka Lung Wu, Rebecca Silbermann, Chang-Ki Min, Marie-Christiane Vekemans, Markus Munder, Ja Min Byun, Joaquín Martínez-Lopez, Madhav V. Dhodapkar
Collection and assembly of data: Naresh Bumma, Hans C. Lee, James E. Hoffman, Attaya Suvannasankha, Jeffrey A. Zonder, Suzanne Lentzsch, Rachid Baz, Joseph J. Maly, Swathi Namburi, Matthew J. Pianko, Jing Christine Ye, Ka Lung Wu, Rebecca Silbermann, Marie-Christiane Vekemans, Markus Munder, Ja Min Byun, Joaquín Martínez-Lopez, Dhruti Chokshi, Anita Boyapati, Anasuya Hazra, L. Andres Sirulnik, Karen Rodriguez Lorenc, Glenn S. Kroog, Yariv Houvras, Madhav V. Dhodapkar
Data analysis and interpretation: Naresh Bumma, Joshua Richter, Sundar Jagannath, Hans C. Lee, James E. Hoffman, Attaya Suvannasankha, Jeffrey A. Zonder, Mansi R. Shah, Suzanne Lentzsch, Rachid Baz, Joseph J. Maly, Swathi Namburi, Matthew J. Pianko, Chang-Ki Min, Markus Munder, Ja Min Byun, Joaquín Martínez-Lopez, Kaniel Cassady, Michelle DeVeaux, Dhruti Chokshi, Anita Boyapati, Anasuya Hazra, George D. Yancopoulos, L. Andres Sirulnik, Karen Rodriguez Lorenc, Glenn S. Kroog, Yariv Houvras
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

A list study investigators can be found in Appendix Table A1 (online only). The study was designed by employees of Regeneron Pharmaceuticals in collaboration with the investigators. The authors thank the patients, their families, all other investigators, and all investigational site members involved in this study. The authors thank Osnat Ben-Shahar, PhD, from Regeneron Pharmaceuticals for assistance with the development and writing of the manuscript. Editorial and studio support was provided by the Oberon business unit

of OPEN Health Communications, and funded by Regeneron Pharmaceuticals Inc, in accordance with Good Publication Practice. Responsibility for all opinions, conclusions, and data interpretation lies with the authors.

REFERENCES

1. Mateos MV, Weisel K, De Stefano V, et al: LocoMMotion: A prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. Leukemia 36:1371-1376, 2022
2. Kumar S, Baizer L, Callander NS, et al: Gaps and opportunities in the treatment of relapsed-refractory multiple myeloma: Consensus recommendations of the NCI Multiple Myeloma Steering Committee. Blood Cancer J 12:98, 2022
3. Podar K, Leleu X: Relapsed/refractory multiple myeloma in 2020/2021 and beyond. Cancers (Basel) 13:5154, 2021
4. Lee HC, Raje NS, Landgren O, et al: Phase 1 study of the anti-BCMA antibody-drug conjugate AMG 224 in patients with relapsed/refractory multiple myeloma. Leukemia 35:255-258, 2021
5. Lee L, Bounds D, Paterson J, et al: Evaluation of B cell maturation antigen as a target for antibody drug conjugate mediated cytotoxicity in multiple myeloma. Br J Haematol 174:911-922, 2016
6. Lancman G, Sastow DL, Cho HJ, et al: Bispecific antibodies in multiple myeloma: Present and future. Blood Cancer Discov 2:423-433, 2021
7. Raje N, Berdeja J, Lin Y, et al: Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. N Engl J Med 380:1726-1737, 2019
8. Berdeja JG, Madduri D, Usmani SZ, et al: Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): A phase 1b/2 open-label study. Lancet 398:314-324, 2021
9. Lonial S, Lee HC, Badros A, et al: Longer term outcomes with single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma: 13-month follow-up from the pivotal DREAMM-2 study. Cancer 127:4198-4212, 2021
10. Moreau P, Garfall AL, van de Donk N, et al: Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med 387:495-505, 2022
11. Lesokhin AM, Tomasson MH, Arnulf B, et al: Elranatamab in relapsed or refractory multiple myeloma: Phase 2 MagnetisMM-3 trial results. Nat Med 29:2259-2267, 2023
12. Munshi NC, Anderson LD Jr, Shah N, et al: Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med 384:705-716, 2021
13. D'Souza A, Shah N, Rodriguez C, et al: A phase I first-in-human study of ABBV-383, a B-cell maturation antigen × CD3 bispecific T-cell redirecting antibody, in patients with relapsed/refractory multiple myeloma. J Clin Oncol 40:3576-3586, 2022
14. Zhang X, Zhang H, Lan H, et al: CAR-T cell therapy in multiple myeloma: Current limitations and potential strategies. Front Immunol 14:1101495, 2023
15. Gust J: BCMA-CAR T-cell treatment–associated parkinsonism. Blood 142:1181-1183, 2023
16. Van Oekelen O, Aleman A, Upadhyaya B, et al: Neurocognitive and hypokinetic movement disorder with features of parkinsonism after BCMA-targeting CAR-T cell therapy. Nat Med 27:2099-2103, 2021
17. Cho SF, Yeh TJ, Anderson KC, et al: Bispecific antibodies in multiple myeloma treatment: A journey in progress. Front Oncol 12:1032775, 2022
18. Raje N, Anderson K, Einsele H, et al: Monitoring, prophylaxis, and treatment of infections in patients with MM receiving bispecific antibody therapy: Consensus recommendations from an expert panel. Blood Cancer J 13:116, 2023
19. Smith EJ, Olson K, Haber LJ, et al: A novel, native-format bispecific antibody triggering T-cell killing of B-cells is robustly active in mouse tumor models and cynomolgus monkeys. Sci Rep 5:17943, 2015
20. Tustian AD, Endicott C, Adams B, et al: Development of purification processes for fully human bispecific antibodies based upon modification of protein A binding avidity. MAbs 8:828-838, 2016
21. DiLillo DJ, Olson K, Mohrs K, et al: A BCMAxCD3 bispecific T cell-engaging antibody demonstrates robust antitumor efficacy similar to that of anti-BCMA CAR T cells. Blood Adv 5:1291-1304, 2021
22. US Food and Drug Administration: Project optimus, in Oncology Center of Excellence (ed): Reforming the Dose Optimization and Dose Selection Paradigm in Oncology, 2023. https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus
23. Rajkumar SV, Dimopoulos MA, Palumbo A, et al: International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 15:e538-e548, 2014
24. Fourie Zirkelbach J, Shah M, Vallejo J, et al: Improving dose-optimization processes used in oncology drug development to minimize toxicity and maximize benefit to patients. J Clin Oncol 40:3489-3500, 2022
25. Lee DW, Santomasso BD, Locke FL, et al: ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 25:625-638, 2019
26. Kumar S, Paiva B, Anderson KC, et al: International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 17:e328-e346, 2016

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Linvoseltamab for Treatment of Relapsed/Refractory Multiple Myeloma

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Naresh Bumma
Consulting or Advisory Role: Janssen, Sanofi
Speakers' Bureau: Sanofi

Joshua Richter
Consulting or Advisory Role: Takeda, Adaptive Biotechnologies, Karyopharm Therapeutics, Antengene, Sanofi, Genentech, Pfizer, Janssen, AbbVie, Bristol Myers Squibb/Celgene, Regeneron
Speakers' Bureau: Celgene, Janssen, Bristol Myers Squibb, Sanofi, Adaptive Biotechnologies
Travel, Accommodations, Expenses: Regeneron

Sundar Jagannath
Consulting or Advisory Role: Bristol Myers Squibb, Janssen, Karyopharm Therapeutics, Legend Biotech, Takeda, Sanofi, Regeneron, Caribou Biosciences
Travel, Accommodations, Expenses: Bristol Myers Squibb, Janssen Biotech, Regeneron

Hans C. Lee
Consulting or Advisory Role: Takeda, GlaxoSmithKline, Sanofi, Bristol Myers Squibb, Genentech, Allogene Therapeutics, AbbVie, Janssen Research & Development, Regeneron
Research Funding: Takeda, Amgen, Janssen, GlaxoSmithKline, Regeneron, Bristol Myers Squibb/Celgene

James E. Hoffman
Stock and Other Ownership Interests: Syndax

Attaya Suvannasankha
Consulting or Advisory Role: Janssen Oncology, GlaxoSmithKline
Research Funding: Janssen Oncology (Inst), GlaxoSmithKline (Inst), BMS (Inst), Regeneron (Inst), Genentech (Inst)
Patents, Royalties, Other Intellectual Property: Novel bone anabolic agent in the treatment of cancer bone metastasis (Inst)

Jeffrey A. Zonder
Employment: Bristol Myers Squibb/Celgene
Consulting or Advisory Role: Takeda, Sanofi/Regeneron
Research Funding: BMS (Inst), Janssen Oncology

Mansi R. Shah
Honoraria: Curio Science, Targeted Oncology
Consulting or Advisory Role: Regeneron, Bristol Myers Squibb Foundation, Janssen Oncology
Research Funding: Janssen (Inst), Bristol Myers Squibb Foundation (Inst), Regeneron (Inst)
Travel, Accommodations, Expenses: Regeneron, Curio Science

Suzanne Lentzsch
This author is an Associate Editor for *Journal of Clinical Oncology*. Journal policy recused the author from having any role in the peer review of this manuscript.
Stock and Other Ownership Interests: Poseida, Dianthus Therapeutics
Consulting or Advisory Role: Janssen, GlaxoSmithKline, Pfizer, BMS, Adaptive Biotechnologies, Sanofi, Karyopharm Therapeutics, Regeneron, Alexion Pharmaceuticals, Bluebird Bio, Crispr Tx, Incyte
Speakers' Bureau: PeerView, Clinical Care Options, BioAscent, RedMedEd.com
Research Funding: Sanofi
Patents, Royalties, Other Intellectual Property: Patent 11-1F4 monoclonal antibody for use in AL Amyloidosis
Travel, Accommodations, Expenses: Regeneron

Rachid Baz
Honoraria: Hikma Pharmaceuticals
Consulting or Advisory Role: BMS, Sanofi, Janssen, Pfizer
Research Funding: Karyopharm Therapeutics (Inst), AbbVie (Inst), Janssen (Inst), BMS (Inst), Daiichi Sankyo/Lilly, Seagen, Regeneron, Zymeworks, Arvinas, Marker Therapeutics, Pionyr, Quantum Leap Healthcare Collaborative
Other Relationship: GlaxoSmithKline

Swathi Namburi
Honoraria: Medscape
Consulting or Advisory Role: Bristol Myers Squibb/Celgene/Juno, Janssen, Sanofi, Bristol Myers Squibb/Celgene/Juno (Inst), Regeneron (Inst), ORIC Pharmaceuticals (Inst)
Open Payments Link: https://openpaymentsdata.cms.gov/physician/650288

Matthew J. Pianko
Consulting or Advisory Role: Janssen Oncology, GlaxoSmithKline, Sanofi, Pfizer
Research Funding: Regeneron (Inst), Nektar (Inst), Pfizer (Inst), Trillium Therapeutics (Inst), Sanofi (Inst), AbbVie (Inst), Bristol Myers Squibb/Celgene (Inst), Janssen (Inst), Ascentage Pharma (Inst), Ipsen (Inst)

Jing Christine Ye
Honoraria: Janssen Scientific Affairs, BMS, Sanofi
Consulting or Advisory Role: BMS, Janssen
Research Funding: Genmab (Inst), GSK (Inst), Celgene (Inst), Regeneron (Inst), MingSight (Inst), Pfizer (Inst), Norvatis (Inst)

Ka Lung Wu
Consulting or Advisory Role: Sanofi, Janssen
Travel, Accommodations, Expenses: Sanofi

Rebecca Silbermann
Consulting or Advisory Role: Sanofi/Aventis, Janssen Oncology, Pfizer
Research Funding: Sanofi
Travel, Accommodations, Expenses: Healthtree

Marie-Christiane Vekemans
Consulting or Advisory Role: Janssen (Inst), Sanofi (Inst), Takeda (Inst), BMS GmbH & Co KG (Inst), Amgen (Inst), Pfizer (Inst)
Travel, Accommodations, Expenses: Janssen (Inst), Sanofi (Inst)

Markus Munder
Honoraria: Janssen Oncology, BMS GmbH & Co KG, GlaxoSmithKline, Sanofi
Consulting or Advisory Role: Janssen Oncology, BMS GmbH & Co KG, GlaxoSmithKline, Sanofi, Takeda, Amgen, Stemline Therapeutics
Travel, Accommodations, Expenses: Amgen, Bristol Myers Squibb

Joaquín Martínez-Lopez
Honoraria: Janssen Oncology, BMSi
Speakers' Bureau: Janssen, Pfizer, BMSi, Amgen
Research Funding: Bristol Myers Squibb/Celgene (Inst)

Kaniel Cassady
Employment: Regeneron
Stock and Other Ownership Interests: Regeneron

Michelle DeVeaux
Employment: Regeneron
Stock and Other Ownership Interests: Regeneron

Dhruti Chokshi
Employment: Regeneron
Stock and Other Ownership Interests: Regeneron, Johnson & Johnson/Janssen, Gilead Sciences, Viatris, Pfizer

Anita Boyapati
Employment: Regeneron
Stock and Other Ownership Interests: Regeneron
Patents, Royalties, Other Intellectual Property: Patent No.: US 11,319,375 B2 and International Patent number (Patent Cooperation Treaty): WO 2024/050466 A1

Anasuya Hazra
Employment: Regeneron
Stock and Other Ownership Interests: Regeneron

George D. Yancopoulos
Employment: Regeneron
Leadership: Regeneron
Stock and Other Ownership Interests: Regeneron
Patents, Royalties, Other Intellectual Property: Multiple patents assigned to regeneron (no personal compensation related to patents above employment)

L. Andres Sirulnik
Employment: Regeneron
Leadership: Regeneron
Stock and Other Ownership Interests: Regeneron

Karen Rodriguez Lorenc
Employment: Regeneron
Stock and Other Ownership Interests: Regeneron

Glenn S. Kroog
Employment: Regeneron
Stock and Other Ownership Interests: Regeneron

Yariv Houvras
Employment: Regeneron
Stock and Other Ownership Interests: Regeneron

Madhav V. Dhodapkar
Consulting or Advisory Role: Roche/Genentech, Lava Therapeutics, Janssen Oncology, Sanofi

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. List of Study Investigators

Country	Site Name	Investigator(s)	Patients Enrolled
The United States	Ohio State University—James Cancer Hospital, Columbus, OH	Naresh Bumma	47
The United States	Icahn School of Medicine at Mount Sinai, New York, NY	Sundar Jagannath, Joshua Richter	38
The United States	Winship Cancer Institute at Emory University, Atlanta, GA	Madhav V. Dhodapkar	24
The United States	University of Miami Sylvester Comprehensive Cancer Center, Miami, FL	James E. Hoffman	20
The United States	University of Texas MD Anderson Clinic, Houston, TX	Hans C. Lee	20
The United States	Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN	Attaya Suvannasankha	19
The United States	Rutgers Cancer Institute of New Jersey, New Brunswick, NJ	Mansi R. Shah	13
The United States	Columbia University Medical Center, New York, NY	Suzanne Lentzsch	12
The United States	Barbara Ann Karmanos Cancer Institute, Detroit, MI	Jeffery A. Zonder	12
The United States	Moffitt Cancer Center, Tampa, FL	Rachid Baz	12
The United States	Norton Cancer Institute, Louisville, KY	Joseph J. Maly	12
The United States	Swedish Cancer Institute, Seattle, WA	Swathi Namburi	11
Belgium	ZNA Psychiatrisch Ziekenhuis Stuivenberg, Antwerp	Ka Lung Wu	9
The United States	University of Michigan Health System, Ann Arbor, MI	Matthew J. Pianko, Jing Christine Ye	8
The United States	Oregon Health & Science University, Portland, OR	Rebecca Silbermann	5
South Korea	The Catholic University of Korea, Seoul, St Mary's Hospital, Seoul	Chang-Ki Min	5
Belgium	Cliniques Universitaires Saint-Luc, Brussels	Marie-Christiane Vekemans	4
Germany	University Medical Center of Johannes Gutenberg-University Mainz, Mainz	Markus Munder	3
South Korea	Seoul National University Cancer Hospital, Seoul	Ja Min Byun	3
Spain	Hospital Universitario 12 de Octubre, Madrid	Joaquín Martínez-Lopez	2
Germany	Universitätsklinikum Essen, Essen	Alexander Carpinteiro	1
South Korea	Yonsei University College of Medicine, Severance Hospital, Seoul	Jin Seok Kim	1
Spain	Hospital de la Santa Creu i Sant Pau, Barcelona	Jordi Lopez Pardo	1
Total			282