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Elranatamab in relapsed or refractory multiple myeloma: the MagnetisMM-1 phase 1 trial

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Nizar J. Bahlis[1], Caitlin L. Costello[2], Noopur S. Raje[3], Moshe Y. Levy[4], Bhagirathbhai Dholaria[5], Melhem Solh[6], Michael H. Tomasson[7], Michael A. Damore[8], Sibo Jiang[9], Cynthia Basu[9], Athanasia Skoura[10], Edward M. Chan[11], Suzanne Trudel[12], Andrzej Jakubowiak[13], Cristina Gasparetto[14], Michael P. Chu[15], Andrew Dalovisio[16], Michael Sebag[17] & Alexander M. Lesokhin[18]

Multiple myeloma (MM) is a plasma cell malignancy expressing B cell maturation antigen (BCMA). Elranatamab, a bispecific antibody, engages BCMA on MM and CD3 on T cells. The MagnetisMM-1 trial evaluated its safety, pharmacokinetics and efficacy. Primary endpoints, including the incidence of dose-limiting toxicities as well as objective response rate (ORR) and duration of response (DOR), were met. Secondary efficacy endpoints included progression-free survival (PFS) and overall survival (OS). Eighty-eight patients with relapsed or refractory MM received elranatamab monotherapy, and 55 patients received elranatamab at efficacious doses. Patients had received a median of five prior regimens; 90.9% were triple-class refractory, 29.1% had high cytogenetic risk and 23.6% received prior BCMA-directed therapy. No dose-limiting toxicities were observed during dose escalation. Adverse events included cytopenias and cytokine release syndrome. Exposure was dose proportional. With a median follow-up of 12.0 months, the ORR was 63.6% and 38.2% of patients achieving complete response or better. For responders, the median DOR was 17.1 months. All 13 patients evaluable for minimal residual disease achieved negativity. Even after prior BCMA-directed therapy, 53.8% achieved response. For all 55 patients, median PFS was 11.8 months, and median OS was 21.2 months. Elranatamab achieved durable responses, manageable safety and promising survival for patients with MM. ClinicalTrials.gov Identifier: NCT03269136.

Multiple myeloma (MM) is an incurable plasma cell malignancy. Clinical outcomes remain poor for patients with relapsed or refractory multiple myeloma (RRMM) after therapy with at least one proteasome inhibitor, one immunomodulatory drug and one CD38-directed antibody[1]. There remains a substantial need to develop novel therapeutic approaches to improve outcomes for patients. B cell maturation antigen (BCMA), a member of the tumor necrosis factor receptor family, represents a promising target due to its downstream signaling through survival

A full list of affiliations appears at the end of the paper. e-mail: nbahlis@ucalgary.ca

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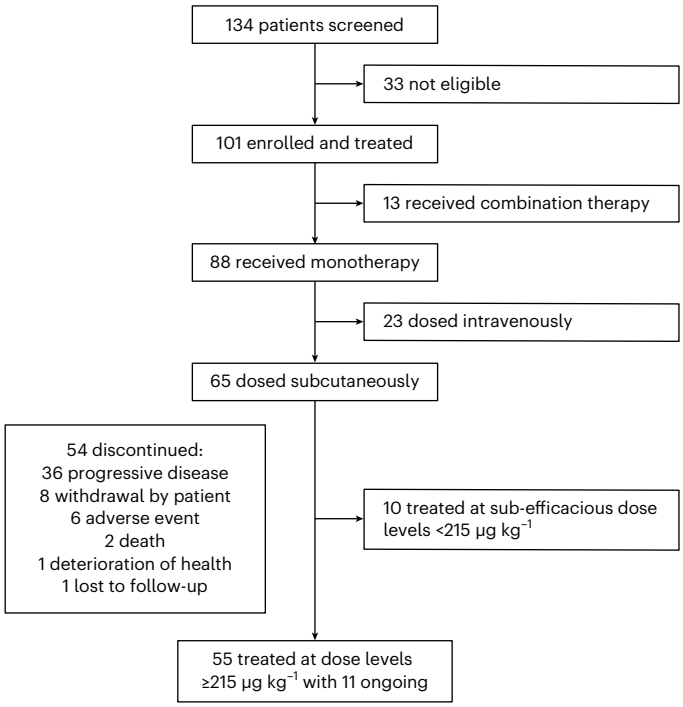

Fig. 1 | CONSORT diagram of MagnetisMM-1.

pathways and its ubiquitous expression on the surface of myeloma cells[2,3]. In addition, soluble BCMA is elevated in the sera of patients with MM and correlates with disease burden and survival[4].

Novel BCMA-directed therapies include antibody–drug conjugates (ADCs), chimeric antigen receptor T cell (CAR-T) therapies and T-cell-engaging bispecific antibodies. In the United States, three BCMA-targeted therapies are currently approved to treat patients with RRMM. Idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), both CAR-T-cell therapies, showed an objective response rate (ORR) of 67.1% (94/140) and 83.2% (94/113), respectively, in patients who underwent leukapheresis[5–7]. Teclistamab, a T-cell-engaging bispecific antibody, demonstrated an ORR of 63.0% (104/165) (refs. 8,9).

Elranatamab (PF-06863135) is a humanized bispecific IgG2 antibody targeting BCMA on myeloma cells and CD3 on T cells. Elranatamab activates and directs T cells to induce a selective cytotoxic T cell response against myeloma cells[10]. In preclinical models, elranatamab induced dose-dependent death of myeloma cell lines and primary patient cells as well as tumor regression in orthotopic myeloma xenograft models[10]. Here we present results from the ongoing first-in-human phase 1 study (MagnetisMM-1) evaluating the safety, pharmacokinetics, pharmacodynamics and efficacy of elranatamab for patients with RRMM. With the exception of safety, this report focuses primarily on evaluating outcomes for 55 patients with RRMM who received single-agent elranatamab subcutaneously at efficacious doses ≥215 μg kg^{-1}.

Results

Trial design and patients

Between 29 November 2017 and 8 April 2021, 134 patients were screened, and 101 were enrolled and received at least one dose of elranatamab (Fig. 1). Of the 101 patients, 88 received elranatamab monotherapy either intravenously (n = 23) or subcutaneously (n = 65). Of the 65 patients who received elranatamab subcutaneously and with a data cutoff of 30 September 2022, 11 patients were ongoing and 54 had discontinued due to progressive disease (n = 36), withdrawal by patient (n = 8), adverse event (n = 6), death (n = 2), deterioration of health (n = 1) or lost to follow-up (n = 1). For subcutaneous monotherapy,

Table 1 | Baseline characteristics and prior treatments

	Elranatamab SC monotherapy (n=55)
Median age, years	64.0 (42–80)
Sex	
Female	26 (47.3)
Male	29 (52.7)
Race	
White	37 (67.3)
Black/African American	11 (20.0)
Asian	4 (7.3)
Not reported	3 (5.5)
ECOG PS	
0–1	50 (90.9)
≥2	5 (9.1)
R-ISS stage at initial diagnosis	
Stage I	14 (25.5)
Stage II	20 (36.4)
Stage III	11 (20.0)
Not reported	10 (18.2)
Cytogenetic risk	
High[a]	16 (29.1)
Standard	35 (63.6)
Unknown	4 (7.3)
Extramedullary disease	17 (30.9)
Median number of prior anti-myeloma therapies	5.0 (2–14)
Triple-class refractory[b]	50 (90.9)
Refractory to last line of therapy	49 (89.1)
Prior PIs	55 (100.0)
Bortezomib	52 (94.5)
Carfilzomib	47 (85.5)
Ixazomib	18 (32.7)
Prior ImiDs	55 (100.0)
Lenalidomide	54 (98.2)
Pomalidomide	52 (94.5)
Thalidomide	9 (16.4)
CC-92480	2 (3.6)
Iberdomide	1 (1.8)
Prior anti-CD38 therapy	54 (98.2)
Daratumumab	52 (94.5)
Isatuximab	4 (7.3)
Other[c]	1 (1.8)
Prior BCMA-targeted therapy	13 (23.6)
Anti-BCMA ADC	4 (7.3)
CAR-T	5 (9.1)
Both anti-BCMA ADC and CAR-T	4 (7.3)

Values are median (range) or n (%). Data cutoff was 30 September 2022. Patients may have received more than one treatment within a given therapy class. [a]Definition of high cytogenetic risk includes t(4;14), t(14;16) and del(17p). [b]Triple-class refractory disease is refractory to at least one PI, one ImiD and one anti-CD38 therapy. [c]One patient treated at 360 μg kg^{-1} received prior anti-myeloma therapy with a CD38×CD3 bispecific molecule. ImiD, immunomodulatory drug; PI, proteasome inhibitor; R-ISS, Revised International Staging System; SC, subcutaneous.

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Table 2 | TEASs (all causality)

Adverse event	Elranatamab SC monotherapy (*n*=55)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hematologic					
Neutropenia	0	2 (3.6)	14 (25.5)	25 (45.5)	41 (74.5)
Anemia	1 (1.8)	8 (14.5)	28 (50.9)	0	37 (67.3)
Lymphopenia	0	1 (1.8)	3 (5.5)	25 (45.5)	29 (52.7)
Thrombocytopenia	6 (10.9)	6 (10.9)	6 (10.9)	10 (18.2)	28 (50.9)
Non-hematologic					
CRS[a]	28 (50.9)	20 (36.4)	0	0	48 (87.3)
Injection site reaction	27 (49.1)	4 (7.3)	0	0	31 (56.4)
Fatigue	7 (12.7)	12 (21.8)	4 (7.3)	0	23 (41.8)
Diarrhea	12 (21.8)	8 (14.5)	2 (3.6)	0	22 (40.0)
Dry skin	18 (32.7)	2 (3.6)	0	0	20 (36.4)
Hypophosphatemia	0	6 (10.9)	13 (23.6)	1 (1.8)	20 (36.4)
Decreased appetite	11 (20.0)	7 (12.7)	1 (1.8)	0	19 (34.5)
Nausea	6 (10.9)	10 (18.2)	3 (5.5)	0	19 (34.5)

Values are *n* (%). Data cutoff was 30 September 2022. Any grade TEAEs reported in more than 33.3% of patients. Grading of TEAEs was based on NCI CTCAE version 4.03, except for CRS. Grading of CRS was based on Lee et al.[13]. [a]Twenty patients received no priming or premedication; 20 patients received priming only; and 15 patients received priming plus premedication. In the group that received priming plus premedication, the overall incidence of CRS was 67% and limited to grade 1 (33%) and grade 2 (33%), with seven (47%) patients receiving tocilizumab. SC, subcutaneous.

10 patients received elranatamab at sub-efficacious dose levels (80 μg kg^{-1} or 130 μg kg^{-1}) not associated with International Myeloma Working Group (IMWG)-confirmed responses of partial response (PR) or better, and 55 patients received elranatamab at efficacious dose levels ≥215 μg kg^{-1}. For these 55 patients, median age was 64 years (range, 42–80) with 29 (52.7%) male and 26 (47.3%) female patients (Table 1). Notably, 17 (30.9%) patients had extramedullary disease, and 16 (29.1%) patients had a high cytogenetic risk at study entry based on local assessment and defined by the presence of detectable t(4;14), t(14;16) or del(17p) abnormalities. These patients had a median of five prior anti-myeloma therapies (range, 2–14), and 38 (69.1%) patients had received prior stem cell transplants. A total of 54 (98.2%) patients had disease that was triple-class exposed, and 50 (90.9%) patients had disease that was triple-class refractory; 43 (78.2%) patients had disease that was penta-drug exposed, and 32 (58.2%) patients had disease that was penta-drug refractory. A total of 13 (23.6%) patients were exposed to prior BCMA-directed therapy, including ADCs in four (7.3%) patients, CAR-T therapy in five (9.1%) patients and both in four (7.3%) patients.

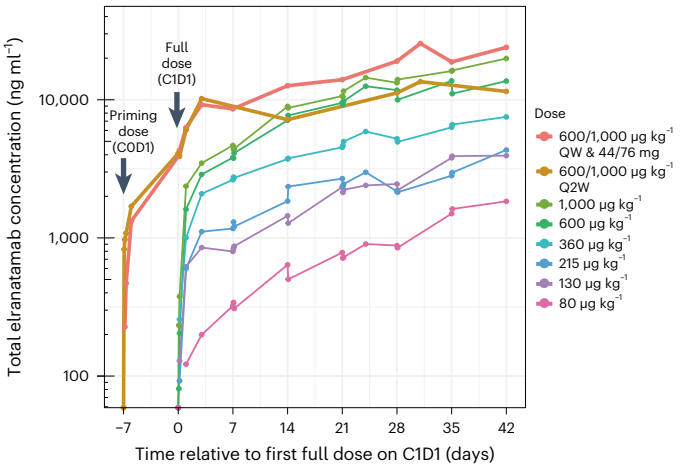

Fig. 2 | Elranatamab pharmacokinetics. A priming dose was not administered during dose escalation (part 1), whereas a single priming dose of 600 μg kg^{-1} (or equivalent 44-mg fixed dose) was administered 1 week before the RP2D during expansions (part 1.1 and part 2A). C, cycle; D, day.

Safety endpoints

Elranatamab monotherapy demonstrated a manageable safety profile (*n* = 88) (Extended Data Table 1). No dose-limiting toxicities (DLTs) were observed during dose escalation (part 1), and the maximum tolerated dose of elranatamab was not reached. Among the 55 patients treated at doses associated with clinical efficacy, the most common treatment-emergent adverse events (TEAEs) regardless of causality (and irrespective of whether priming and premedication were implemented) included cytopenias, cytokine release syndrome (CRS) and injection site reaction (*n* = 55) (Table 2). Hematologic TEAEs were common and included neutropenia in 41 (74.5%), anemia in 37 (67.3%), lymphopenia in 29 (52.7%) and thrombocytopenia in 28 (50.9%) patients. The most common (≥50%) non-hematologic TEAEs were CRS in 48 (87.3%) patients and injection site reaction in 31 (56.4%) patients. CRS was limited to grades 1 and 2, with median time to onset of 1.0 d (range, 1.0–3.0) and a median duration of 3.0 d (range, 1.0–10.0); no grade ≥3 events were observed. For patients who received a priming dose of elranatamab, CRS occurred primarily with the priming dose; only two (6.1%) patients experienced grade 1 CRS after receiving the recommended phase 2 dose (RP2D). Among the 15 patients who received both a priming dose and dexamethasone-based premedication in part 2A, the overall incidence of CRS was reduced to 10 (66.7%) patients and limited to grade 1 in five (33.3%) patients and grade 2 in five (33.3%) patients; no grade ≥3 events were observed (Extended Data Table 2).

In addition to the most common TEAEs, other adverse events were reported. Immune effector cell-associated neurotoxicity syndrome (ICANS) was limited to grade 1 in four (7.3%) patients and grade 2 in five (9.1%) patients; no grade ≥3 events were observed. Among the 15 patients who received both a priming dose and dexamethasone-based premedication in part 2A, ICANS was limited to grade 1 in one (6.7%) patient and grade 2 in one (6.7%) patient; no grade ≥3 events were observed (Extended Data Table 3). Infections of any etiology (including

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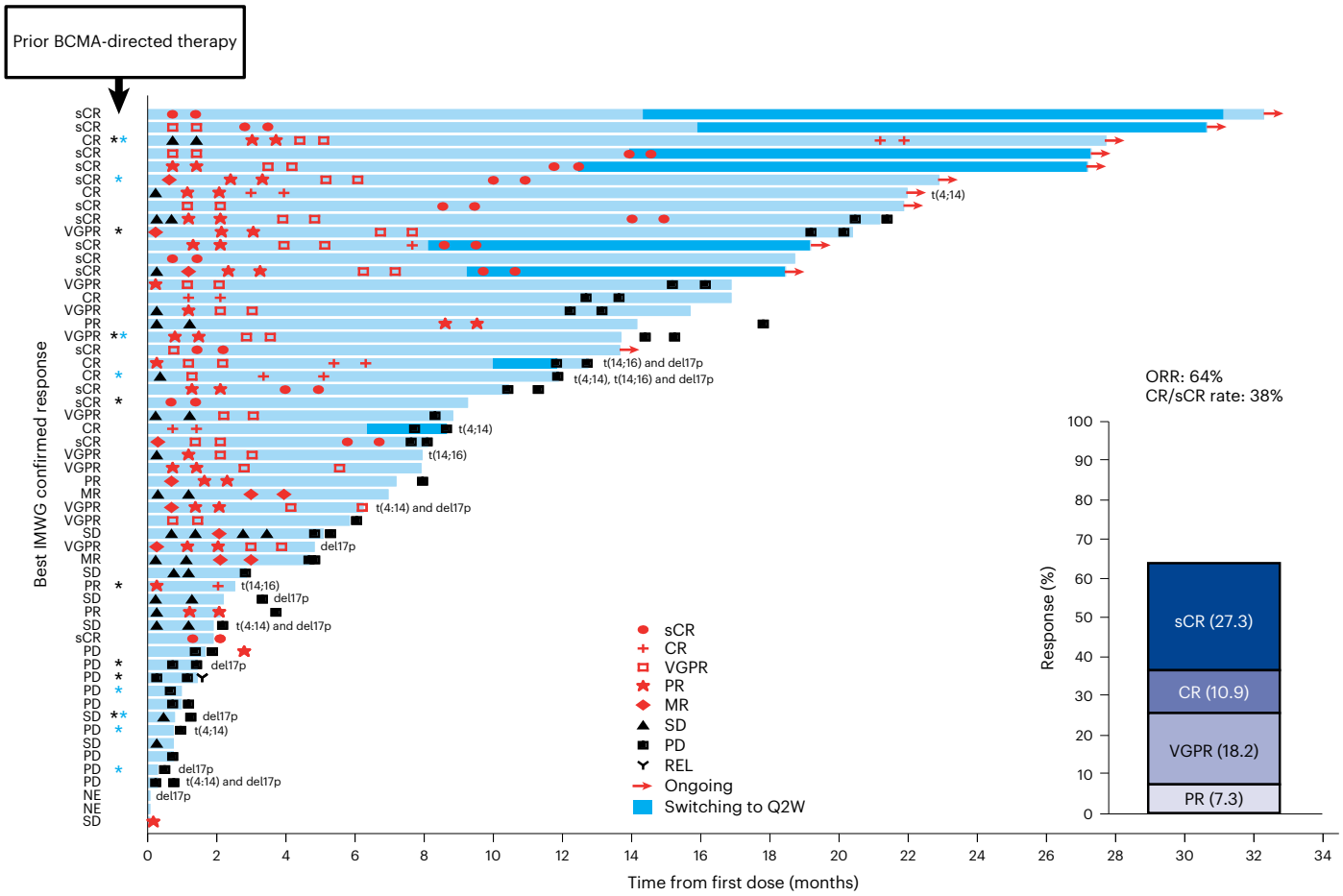

Fig. 3 | Best overall response and duration of treatment. Swimmer plot depicts disease assessments relevant to first response, confirmation of response, deepening of response and best response. Black asterisk indicates prior anti-BCMA ADC. Blue asterisk indicates prior BCMA-targeted CAR-T. MR, minimal response; NE, not evaluable; PD, progressive disease; REL, relapse; SD, stable disease.

bacterial, viral and fungal) or grade were reported in 41 (74.5%) patients, with grade 3 events in 12 (21.8%) and grade 4 events in three (5.5%) patients. Among the 55 patients, 18 (32.7%) received intravenous immunoglobulin. Opportunistic infections occurred in five (9.1%) patients and included pneumocystis jirovecii pneumonia ($n = 2$, both grade 2), adenovirus infection ($n = 1$, grade 5), cytomegalovirus infection ($n = 1$, grade 2), cytomegalovirus infection reactivation ($n = 1$, grade 1) and pneumonia cytomegaloviral ($n = 1$, grade 1). There were eight (14.5%) deaths considered unrelated to study treatment, including three (5.5%) due to disease progression, two (3.6%) due to coronavirus disease 2019 (COVID-19) infection and one each due to plasma cell myeloma, sudden death and septic shock; one death due to adenovirus infection was assessed as related to study treatment. A total of eight (14.5%) patients discontinued treatment due to an adverse event, including one patient with pre-existing peripheral neuropathy who developed muscular weakness assessed as related to study treatment.

Pharmacokinetics and pharmacodynamics

Elranatamab demonstrated linear pharmacokinetics and low incidence of immunogenicity. Elranatamab concentrations over time (Fig. 2) and pharmacokinetic parameters (Extended Data Table 4) are summarized across all subcutaneous dose levels from 80 μg kg^{-1} to 1,000 μg kg^{-1}. Elranatamab showed prolonged absorption, and exposure increased in a dose-proportional manner. A dose of 1,000 μg kg^{-1} every 2 weeks (Q2W) achieved exposure between that observed for 360 μg kg^{-1} once weekly (QW) and 1,000 μg kg^{-1} QW, which were associated with anti-myeloma activity. After subcutaneous dosing, 8.6% (5/58) of patients evaluable for immunogenicity showed treatment-induced anti-drug antibodies (ADAs), including one patient with neutralizing antibodies. All but one patient with ADAs had low titer (close to the minimum required dilution), and no patients who received elranatamab at the RP2D (1,000 μg kg^{-1} or 76 mg QW) developed ADAs.

Serum cytokines, including those produced by activated T cells, were increased after the first dose of elranatamab. Consistent with mitigation of clinical CRS, elevated serum levels of cytokines, including interferon-gamma, interleukin-2, tumor necrosis factor-alpha and interleukin-6, were observed in part 1.1 after the priming dose but then substantially attenuated at the RP2D (Extended Data Fig. 1a–d). Notably, the addition of dexamethasone-based premedication in part 2A reduced cytokine production associated with the priming dose.

Efficacy endpoints

Elranatamab demonstrated anti-myeloma activity and achieved durable clinical and molecular responses. During dose escalation (part 1), the ORR was 50.0% (2/4) at 215 μg kg^{-1}, 75.0% (3/4) at 360 μg kg^{-1}, 66.7% (4/6) at 600 μg kg^{-1} and 83.3% (5/6) at 1,000 μg kg^{-1}. No confirmed responses of PR or better were observed at dose levels less than 215 μg kg^{-1}, including the two lowest subcutaneous dose levels (80 μg kg^{-1} and 130 μg kg^{-1}) or the intravenous dose levels (all ≤50 μg kg^{-1}). The RP2D of 1,000 μg kg^{-1} was established based on an integrated assessment of safety, pharmacokinetics, pharmacodynamics and efficacy. For the 55 patients treated with single-agent elranatamab at efficacious dose levels ≥215 μg kg^{-1}, median duration of follow-up was 12.0 months (range, 0.3–32.3). Overall, the ORR was

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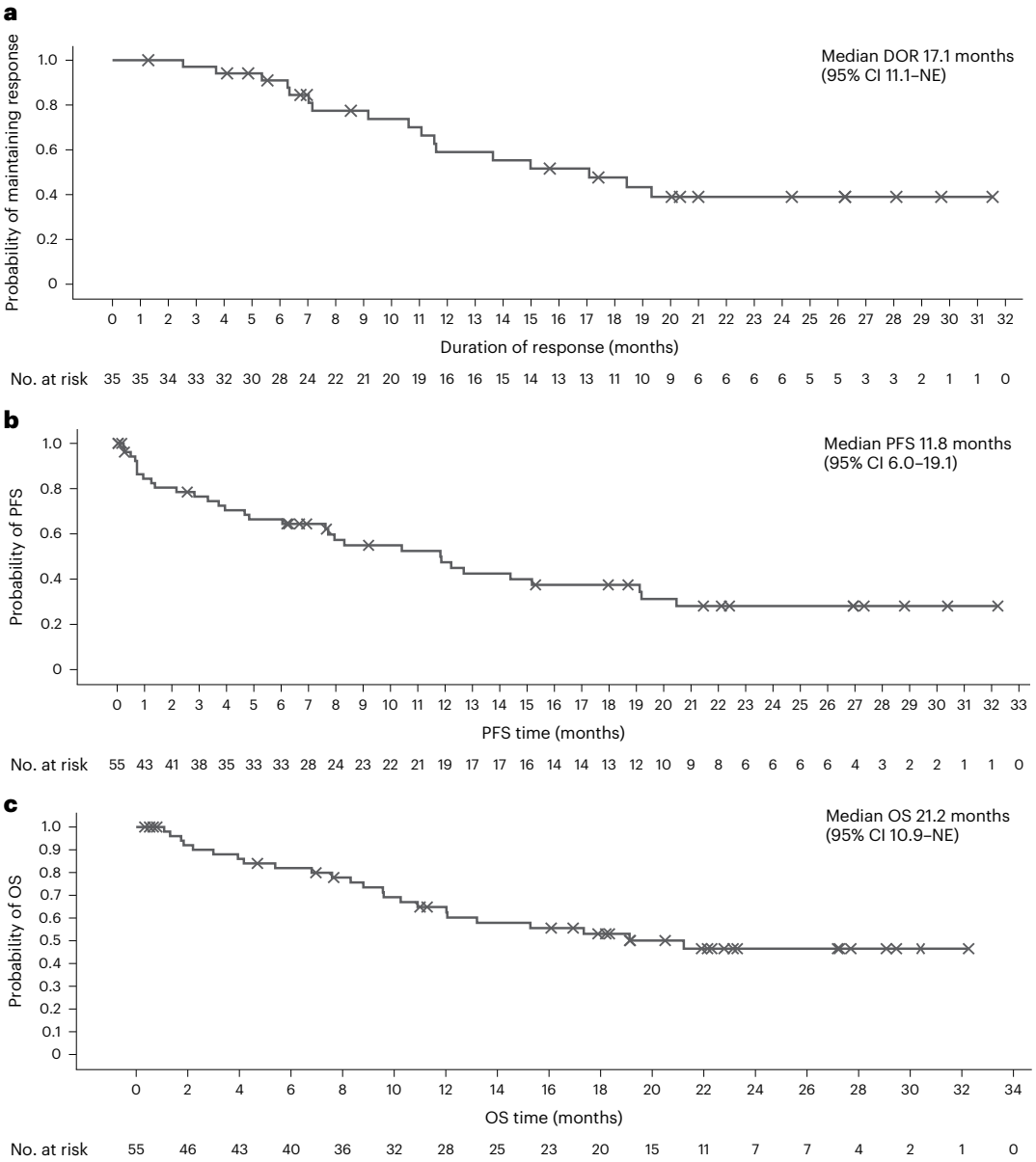

Fig. 4 | Kaplan–Meier plot. a–c, Kaplan–Meier plot. for DOR (**a**), PFS (**b**) and OS (**c**). NE, not estimable.

63.6% (35/55; 95% confidence interval (CI): 50.4–75.1) with 56.4% (31/55) of patients achieving very good partial response (VGPR) or better and 38.2% (21/55) of patients achieving complete response (CR) or better (Fig. 3). Specifically, 27.3% (15/55) of patients achieved confirmed stringent complete responses (sCRs); 10.9% (6/55) achieved confirmed CR; 18.2% (10/55) achieved confirmed VGPR; and 7.3% (4/55) achieved confirmed PR. Serum levels of soluble BCMA, a potential surrogate for disease burden, decreased over time in responding patients (Extended Data Fig. 2). Among 13 patients with prior BCMA-directed therapy, five patients were refractory, and eight patients had received either ADC ($n = 5$) or CAR-T ($n = 3$) immediately before elranatamab therapy. Notably, 53.8% (7/13) of patients with prior BCMA-directed therapy achieved confirmed responses (two sCR, two CR, two VGPR and one PR), including four patients with prior BCMA-directed therapy immediately before elranatamab therapy. Across all 35 responders, median time to first confirmed response of PR or better was 36.0 d (range, 7–262), and median duration of response (DOR) was 17.1 months (95% CI: 11.1–not estimable) (Fig. 4a). Of the eight responders who transitioned to less frequent (Q2W) dosing after ≥6 months of QW therapy, 75.0% (6/8) remained on elranatamab therapy and maintained or deepened response with time. All patient subgroups benefited from elranatamab therapy, with a trend toward lower benefit among those with high cytogenetic risk, extramedullary disease, more than 50% plasma cells in bone marrow or prior BCMA-directed therapy (Extended Data Fig. 3). For all 55 patients, median progression-free survival (PFS) was 11.8 months (95% CI: 6.0–19.1) (Fig. 4b), and median overall survival (OS) was 21.2 months (95% CI: 10.9–not estimable) (Fig. 4c).

A total of 13 patients with confirmed CR or better had a dominant variable (V)–diversity (D)–joining (J) or VJ sequence at baseline and were, therefore, minimal residual disease (MRD) evaluable (Fig. 5). Notably, all 13 (100.0%) patients achieved MRD negativity at a sensitivity of 1×10^{-5}, and nine (69.2%) patients with confirmed CR or better achieved MRD negativity at the 1-month assessment. Molecular responses were durable, and eight (61.5%) patients had sustained MRD negativity beyond 6 months, including two (15.4%) patients with ongoing sCR beyond 2 years.

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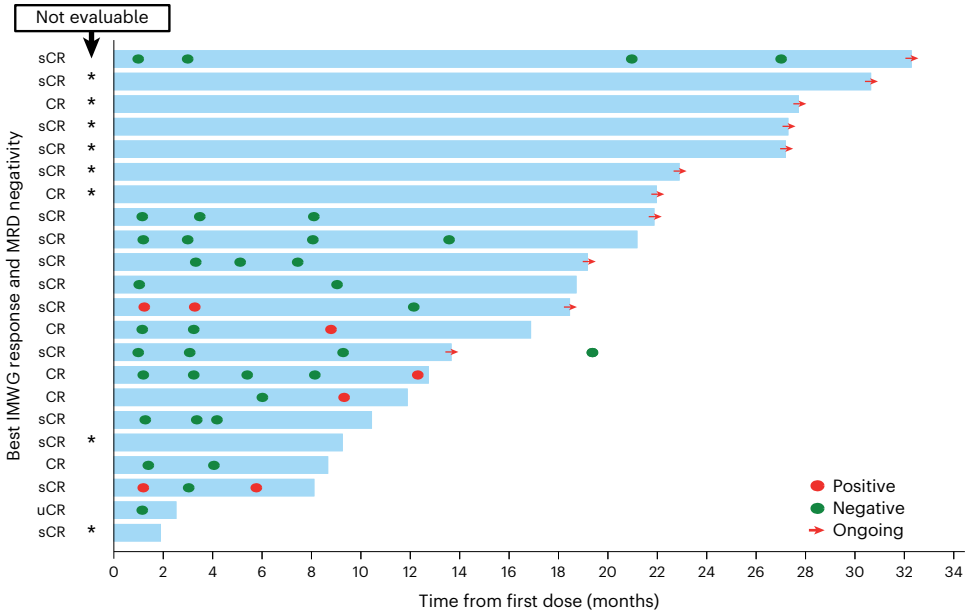

Fig. 5 | Duration of treatment and molecular response for patients achieving CR or sCR. MRD status was assessed by next-generation sequencing at a sensitivity of 1×10^{-5} in accordance with IMWG criteria. Evaluable patients had a dominant VDJ or VJ sequence at baseline and confirmed response of CR or better. Black asterisk indicates 'not evaluable'. u, unconfirmed.

Discussion

MagnetisMM-1 is the first-in-human phase 1 study of elranatamab for patients with RRMM. The RP2D of 1,000 μg kg^{-1} (equivalent to fixed dose of 76 mg) is supported by available data on safety, pharmacokinetics, pharmacodynamics and efficacy. Among 55 patients with RRMM who were heavily pretreated and who received single-agent elranatamab subcutaneously at efficacious doses ≥215 μg kg^{-1}, the ORR was 63.6%, with 38.2% of patients achieving CR or better. Notably, 90.9% of these patients were triple-class refractory. Elranatamab induced rapid and durable responses, with half of responders maintaining response for more than 17 months. This benefit extended to patients with prior BCMA-directed therapy and across all subgroups, with response rates of ≥50% for those with high cytogenetic risk, extramedullary disease or more than 50% bone marrow plasmacytosis. For patients with confirmed CR or better who were MRD evaluable, all 13 patients achieved MRD negativity, and more than 65% of them achieved MRD negativity at the 1-month assessment. Elranatamab-induced durable molecular responses and sustained MRD negativity beyond 6 months were documented for more than 60% of MRD-evaluable patients. These results are particularly notable in the context of an emerging body of evidence linking MRD status to survival[11]. In addition to inducing durable clinical and molecular responses, patients with RRMM who received elranatamab achieved a median PFS of 11.8 months and a median OS of 21.2 months.

Elranatamab demonstrated a manageable safety profile. DLTs were not observed during dose escalation, and a maximum tolerated dose was not reached. The most common TEAEs regardless of causality included CRS and cytopenias. With premedication and a single priming dose, the overall incidence of CRS was reduced to 66.7% and divided equally between grade 1 and grade 2, with no grade ≥3 events. Similarly, the overall incidence of ICANS was reduced to 13.3% and divided equally between grade 1 and grade 2, with no grade ≥3 events. Notably, subsequent studies with elranatamab implemented a step-up priming dose regimen (12 mg on day 1 and 32 mg on day 4) to further mitigate CRS and ICANS. In the present study, infections were common, and grade 3 and grade 4 events occurred in 21.8% and 5.5% of patients, respectively. These results highlight the importance of patient education, preventive measures[12], regular monitoring and prompt diagnosis and treatment for infection.

Elranatamab showed predictable pharmacokinetics and low immunogenicity. Exposure increased in a dose-dependent manner and, consistent with maintenance or deepening of response after transition to less frequent (Q2W) dosing after ≥6 months of QW therapy, a dose of 1,000 μg kg^{-1} Q2W achieved exposure in the range associated with anti-myeloma activity. The overall incidence of treatment-induced ADAs was 8.6%, and no patients who received elranatamab at the RP2D QW developed ADAs.

Immunotherapeutic approaches, including both T-cell-engaging bispecific antibodies and CAR-T therapies, have provided important new opportunities for the treatment of patients with MM. Elranatamab represents a readily accessible off-the-shelf therapy with flexibility for biweekly dosing and provides an option for patients requiring immediate treatment or unable to access CAR-T therapies. Results from MagnetisMM-1 support the favorable risk–benefit profile of elranatamab and highlight a particularly compelling combination of attributes even among these emerging immunotherapies[5–8]. In general, CAR-T therapies have response rates in RRMM similar to (ide-cel, 67.1%) or better than (cilta-cel, 83.2%) those achieved by bispecific molecules (teclistamab, 63.0%; elranatamab, 63.6%) but with higher overall incidence (and severity) of toxicities, including CRS (ide-cel, 83.6% and cilta-cel, 94.8%; versus teclistamab, 72.1% and elranatamab, 66.7%). MRD negativity rates among MRD-evaluable patients were high for all four therapies: elranatamab 100.0% (13/13), ide-cel 100.0% (33/33), cilta-cel 94.3% (33/35) and teclistamab 81.5% (44/54). Although there are inherent limitations to comparisons across studies, additional efficacy endpoints for RRMM have been reported, with a median follow-up of approximately 1 year for elranatamab in this first-in-human phase 1 study (MagnetisMM-1) and for two currently approved BCMA-targeted immunotherapies including teclistamab and ide-cel (Extended Data Table 5). Median DOR for elranatamab (17.1 months) was similar to that for teclistamab (18.4 months) and longer than that for ide-cel (10.7 months). Median PFS for elranatamab (11.8 months) was similar to that for teclistamab (11.3 months) and numerically longer than that for ide-cel (8.8 months). Median OS for elranatamab (21.2 months) was similar to that for teclistamab (18.3 months) and ide-cel (19.4 months). These results demonstrate not only the ways in which immunotherapeutic approaches have extended the range of options for patients with

RRMM but also the importance of customizing therapy to maximize efficacy and minimize toxicity for individual patients.

The interpretation of the results in this study is limited by its single-arm design and lack of direct comparison with other treatment options as well as by the small sample size in some subgroups. However, elranatamab induced durable clinical and molecular responses with predictable pharmacokinetics and a manageable safety profile for patients with RRMM. These results, along with emerging evidence for both PFS and OS, support the favorable risk–benefit profile of elranatamab at its RP2D (76 mg subcutaneously weekly) for patients with RRMM. Ongoing studies, including the pivotal phase 2 study (MagnetisMM-3), will further investigate elranatamab for patients with RRMM or newly diagnosed MM.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-023-02589-w.

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[1]Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada. [2]Moores Cancer Center, University of California, San Diego, La Jolla, CA, USA. [3]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA. [4]Department of Medical Oncology, Baylor Scott and White Health, Dallas, TX, USA. [5]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA. [6]Blood and Marrow Transplant Group of Georgia, Northside Hospital, Atlanta, GA, USA. [7]Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA. [8]Oncology Research and Development, Pfizer Inc., San Diego, CA, USA. [9]Early Clinical Development, Pfizer Inc., San Diego, CA, USA. [10]Early Clinical Development, Pfizer Inc., Collegeville, PA, USA. [11]Oncology Research and Development, Pfizer Inc., South San Francisco, CA, USA. [12]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada. [13]Department of Medicine, University of Chicago Medical Center, Chicago, IL, USA. [14]Department of Medicine, Duke University Cancer Institute, Durham, NC, USA. [15]Cross Cancer Institute, Edmonton, AB, Canada. [16]Department of Hematology and Oncology, Ochsner Health, New Orleans, LA, USA. [17]Cedars Cancer Center, McGill University Health Center, Montreal, QC, Canada. [18]Division of Hematology and Oncology, Memorial Sloan Kettering Cancer Center/Weill Cornell Medical College, New York, NY, USA. ✉e-mail: nbahlis@ucalgary.ca

Methods

Study design and participants

MagnetisMM-1 is a first-in-human, open-label, multicenter, phase 1 study (NCT03269136) that enrolled patients from November 2017 through April 2021 at 14 investigative centers (11 in the United States and three in Canada). The study included intravenous and subcutaneous dose escalation without priming or premedication (part 1), expansions with priming but no premedication (part 1.1) and expansion with both priming and premedication (part 2A). Eligible patients aged ≥18 years had a diagnosis of MM as defined by IMWG criteria[14], measurable disease and progression or intolerance to standard therapies, including at least one proteasome inhibitor, immunomodulatory drug and CD38-directed antibody. Prior BCMA-targeted therapy was permitted. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1 or 2 (if due to underlying MM) as well as adequate hepatic (total bilirubin ≤2.0 mg dl^{-1} with exception for Gilbert syndrome; alkaline phosphatase and aspartate/alanine aminotransferases ≤2.5 times the upper limit of normal with exceptions for bone or liver involvement by tumor, respectively), renal (creatinine clearance ≥30 ml min^{-1}) and hematopoietic (absolute neutrophil count ≥1,000 mm^3, platelet count ≥25,000 mm^3 and hemoglobin ≥8.0 g dl^{-1}) function were required.

This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice. All patients provided written informed consent. The study protocol and relevant documents were approved by an independent institutional review board or ethics committee at each investigative center. Patient safety was monitored jointly by investigators and a safety assessment committee established by the sponsor.

Procedures

Patients received elranatamab monotherapy intravenously (dose levels 0.1, 0.3, 1, 3, 10, 30 or 50 μg kg^{-1}) or subcutaneously (dose levels 80, 130, 215, 360, 600 or 1,000 μg kg^{-1}) either QW or Q2W until disease progression, withdrawal of consent, death or discontinuation. To mitigate CRS, a single priming dose (600 μg kg^{-1} or equivalent 44-mg fixed dose) was administered to patients who received elranatamab at the RP2D (1,000 μg kg^{-1} or equivalent 76-mg fixed dose) in part 1.1 ($n = 20$) and part 2A ($n = 15$). In addition, patients enrolled in part 2A received premedication (dexamethasone 20 mg or equivalent, antihistamine and antipyretic) before the priming dose and the first full treatment dose. Dose modifications were permitted for management of adverse events. Patients with disease stability for ≥2 months were permitted to transition to elranatamab Q2W after 6 months of QW therapy.

Outcomes

For dose escalation (part 1), the primary endpoint was the number of DLTs. The primary efficacy endpoints were ORR and DOR for patients treated at efficacious doses, with response assessed according to IMWG criteria[15]. Secondary endpoints included adverse events, laboratory abnormalities, ORR, time to response, CR rate, DOR, PFS, OS, rate of MRD negativity, pharmacokinetic parameters, immunogenicity and levels of serum cytokines. Additional planned secondary endpoints not reported in this manuscript included above-described endpoints in patients treated with elranatamab in combination with immunomodulatory agents. Exploratory endpoints included levels of soluble BCMA and characterization of immune cells in whole blood and bone marrow by flow cytometry analysis.

The DLT observation period was through the end of the first treatment cycle for each patient in part 1. TEAEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Both CRS and ICANS were defined and graded according to American Society for Transplantation and Cellular Therapy consensus criteria[13]. Tumor response and disease progression were assessed according to IMWG response criteria[15], and ORR was calculated based on confirmed responses reported by investigators. MRD at a sensitivity of 1×10^{-5} was centrally assessed by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) according to IMWG response criteria[15]. Pharmacokinetics, cytokines, lymphocyte subsets and serum levels of soluble BCMA were analyzed over time.

Statistical analysis

Safety and efficacy were evaluated in all patients enrolled who received at least one dose of elranatamab. Elranatamab dose escalation was guided using a Bayesian method with modified Toxicity Probability Interval design[16]. Maximum tolerated dose was defined as the dose with approximately 25% probability of DLT and considers equivalent doses that yield a probability of DLT in the (equivalence) interval between 20% and 30%. Due to the dynamic nature of the Bayesian allocation procedure, the sample size of the modified toxicity probability interval could not be determined in advance. No formal hypothesis testing was performed for efficacy endpoints.

Summary statistics for categorical variables were reported with mean (s.d.) or median (95% CI or range) unless otherwise specified. Time-to-event endpoints were analyzed using the Kaplan–Meier method[17]. CIs for medians were calculated according to the Clopper–Pearson method[18], and CIs for Kaplan–Meier estimates were derived using the log(−log) method[19]. SAS version 9.4 software was used for statistical analysis. This ongoing study is registered with ClinicalTrials.gov (NCT03269136).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Upon reasonable request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information. The protocol and statistical analysis plan for MagnetisMM-1 have been uploaded to ClinicalTrials.gov.

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Author contributions

All authors participated in study design and conduct, in data acquisition, analysis and interpretation and in drafting and revising

the manuscript; and all authors approved the final version before submission. C.B. performed statistical analyses. A.S. and E.M.C. verified the underlying data. S.J. verified the pharmacokinetic and immunogenicity data. M.A.D. verified the pharmacodynamic data. All authors had access to the study data and had final responsibility for the decision to submit the manuscript for publication. A medical writer assisted in manuscript preparation, with funding from the sponsor.

Competing interests

N.J.B. received grant support from Celgene and Janssen; consulting fees from Janssen, Celgene, Amgen, Sanofi, Takeda, Pfizer and Karyopharm Therapeutics; and honoraria from Celgene, Janssen, AbbVie, Amgen, Sanofi, Takeda, Karyopharm Therapeutics, GlaxoSmithKline and Genentech/Roche. C.L.C. received grant support from Takeda, Celgene and Janssen and consulting fees and honoraria from Celgene, Janssen, Pfizer and Takeda. N.S.R. received grant support from Two Seventy Bio; consulting fees and honoraria from Amgen, Bristol Myers Squibb, Celgene, Janssen, Merck, GlaxoSmithKline and Takeda; and honoraria from Research to Practice and Medscape. M.Y.L. received grant support, consultancy and honoraria from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Janssen, Karyopharm Therapeutics, Sanofi, Seattle Genetics and Takeda. B.D. received institutional grant support from Takeda, Janssen, Angiocrine, Pfizer, Poseida, Orca Bio, Molecular Template, Bristol Myers Squibb and MEI Pharma and consulting fees from Jazz Pharmaceuticals, Arivan Research and Gamida Cell. M.S. received grant support from ADCT Therapeutics and Partner Therapeutics; consulting fees and honoraria from Bristol Myers Squibb, Seattle Genetics and Pfizer; and honoraria from GlaxoSmithKline, Bristol Myers Squibb and Amgen. M.A.D., S.J., C.B., A.S. and E.M.C. are employed by Pfizer and hold stock or stock options in Pfizer. S.T. received grant support from Amgen, Bristol Myers Squibb, Genentech, GlaxoSmithKline, Janssen and Pfizer; consulting fees from Amgen, Bristol Myers Squibb and GlaxoSmithKline; and honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, Janssen, Karyopharm Therapeutics, Pfizer, Sanofi and Takeda. A.J. received consulting fees and honoraria and holds membership on boards of directors or advisory committees for AbbVie, Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Karyopharm Therapeutics, Millennium, Sanofi, SkylineDx and Takeda. C.G. received grant support from Celgene; consulting fees and honoraria from Bristol Myers Squibb, Celgene and Janssen; and honoraria from Takeda. M.P.C. received grant support from Celgene and Bristol Myers Squibb and consulting fees and honoraria from Amgen, AstraZeneca, Celgene/Bristol Myers Squibb, Gilead, Janssen and Teva. M.S. received grant support from Janssen and consulting fees and honoraria from Bristol Myers Squibb, Takeda, Novartis, Karyopharm Therapeutics, Sanofi and Amgen. A.M.L. received institutional grant support from Bristol Myers Squibb, Genentech, Trillium Therapeutics, Sanofi, Pfizer and Janssen Oncology; consulting fees and honoraria from Bristol Myers Squibb, Pfizer and Trillium Therapeutics; honoraria from Bristol Myers Squibb, Genmab, Amgen and Janssen; and patents/royalties from Serametrix. M.H.T. and A.D. declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-023-02589-w.

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Correspondence and requests for materials should be addressed to Nizar J. Bahlis.

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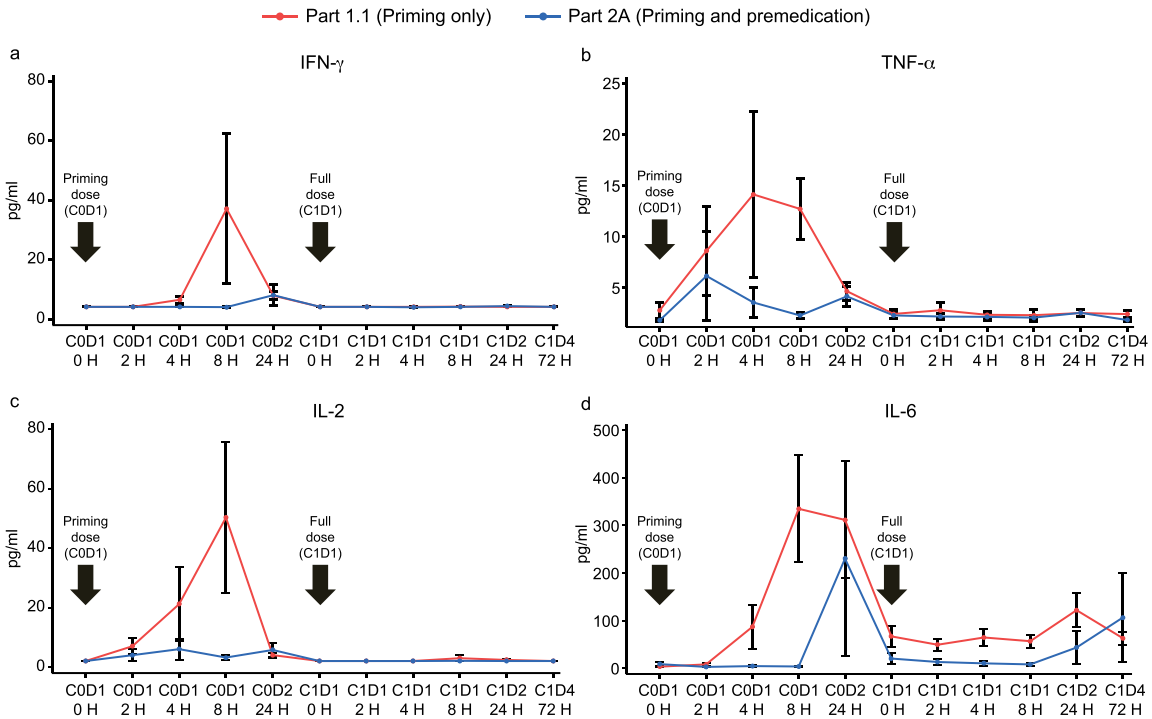

Extended Data Fig. 1 | Effect of premedication on cytokine production including (a) IFN-γ, (b) TNF-α, (c) IL-2, and (d) IL-6. The mean is plotted from 20 patients in Part 1.1 and 15 patients in Part 2A. Error bars represent standard error of the mean. C, cycle; D, day; H, hour; IFN-γ, interferon-gamma; IL-2, interleukin 2; IL-6, interleukin 6; TNF-α, tumor necrosis factor-alpha.

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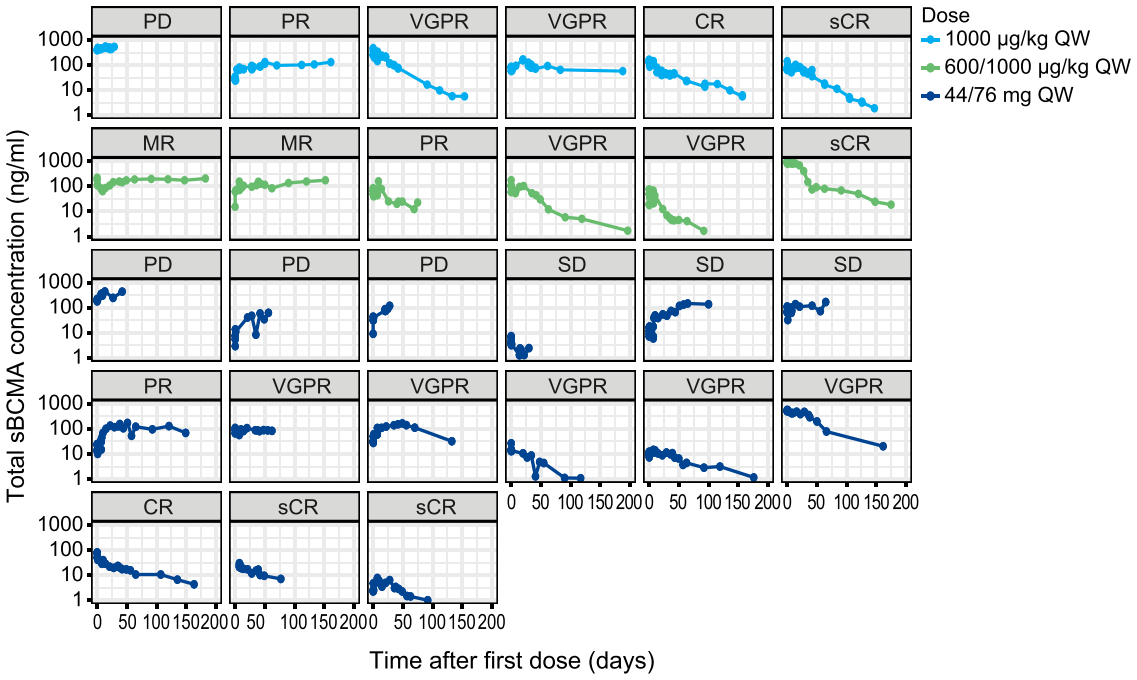

Extended Data Fig. 2 | Elranatamab-induced changes in soluble BCMA. BCMA, B-cell maturation antigen; CR, complete response; MR, minimal response; PD, progressive disease; PR, partial response; QW, once weekly; sBCMA, soluble B-cell maturation antigen; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

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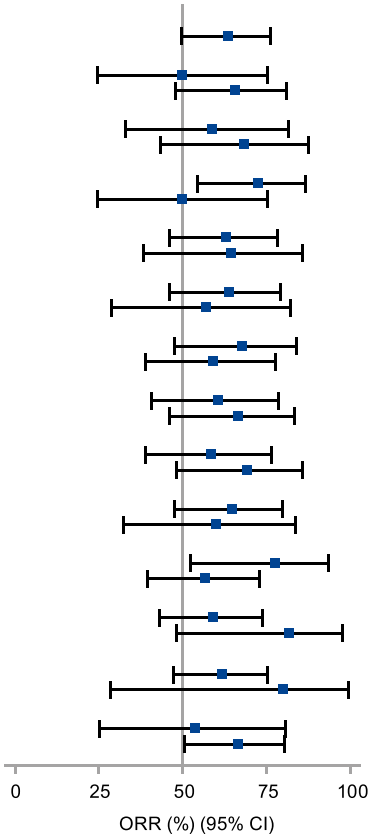
Subgroup	Responders (*n*)/ Participants (*N*)	ORR (%) (95% CI)
All participants	35/55	63.6 (49.6–76.2)
Baseline cytogenetics		
High risk	8/16	50.0 (24.7–75.3)
Not high risk	23/35	65.7 (47.8–80.9)
Baseline extramedullary disease		
Yes	10/17	58.8 (32.9–81.6)
No	13/19	68.4 (43.4–87.4)
Baseline bone marrow plasma cells		
<50%	24/33	72.7 (54.5–86.7)
≥50%	8/16	50.0 (24.7–75.3)
Prior stem cell transplant		
Yes	24/38	63.2 (46.0–78.2)
No	11/17	64.7 (38.3–85.8)
Current disease stage		
1–2	23/36	63.9 (46.2–79.2)
3	8/14	57.1 (28.9–82.3)
Number of prior lines		
≤5	19/28	67.9 (47.6–84.1)
>5	16/27	59.3 (38.8–77.6)
Age (years)		
<65	17/28	60.7 (40.6–78.5)
≥65	18/27	66.7 (46.0–83.5)
Sex		
Male	17/29	58.6 (38.9–76.5)
Female	18/26	69.2 (48.2–85.7)
Race		
White	24/37	64.9 (47.5–79.8)
Other	9/15	60.0 (32.3–83.7)
Renal function		
CrCl ≤60 ml/min	14/18	77.8 (52.4–93.6)
CrCl >60 ml/min	21/37	56.8 (39.5–72.9)
Liver function		
Normal	26/44	59.1 (43.2–73.7)
Impaired	9/11	81.8 (48.2–97.7)
ECOG PS		
0–1	31/50	62.0 (47.2–75.3)
2–3	4/5	80.0 (28.4–99.5)
Prior BCMA-directed therapy		
Yes	7/13	53.8 (25.1–80.8)
No	28/42	66.7 (50.5–80.4)



Extended Data Fig. 3 | Objective response rate across subgroups. Square denotes ORR and the whiskers indicate 95% CI (Clopper-Pearson). Liver function: normal = AST and total bilirubin ≤ULN; impaired = AST or total bilirubin >ULN (including both AST and total bilirubin >ULN). AST, aspartate aminotransferase; BCMA, B-cell maturation antigen; CI, confidence interval; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; ULN, upper limit of normal.

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Extended Data Table 1 | TEAEs (all causality)

Adverse event	Elranatamab IV and SC monotherapy (*N* = 88)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hematologic					
Anemia	2 (2.3)	13 (14.8)	42 (47.7)	1 (1.1)	58 (65.9)
Neutropenia	2 (2.3)	3 (3.4)	19 (21.6)	26 (29.5)	50 (56.8)
Lymphopenia	0	1 (1.1)	11 (12.5)	33 (37.5)	45 (51.1)
Thrombocytopenia	10 (11.4)	8 (9.1)	11 (12.5)	16 (18.2)	45 (51.1)
Non-hematologic					
CRS[a]	37 (42.0)	26 (29.5)	0	0	63 (71.6)
Injection-site reaction	30 (34.1)	4 (4.5)	0	0	34 (38.6)
Fatigue	10 (11.4)	18 (20.5)	4 (4.5)	0	32 (36.4)

Values are *n* (%). Data cutoff was September 30, 2022. Any grade TEAEs reported in >33.3% of patients. Grading of TEAEs based on NCI CTCAE version 4.03, except for CRS. Grading of CRS based on Lee, D.W. et al. *Biol Blood Marrow Transplant* **25**, 625-638 (2019).

[a]53 patients received no priming or premedication, 20 patients received priming only, and 15 patients received priming plus premedication; in the group that received priming plus premedication, the overall incidence of CRS was 67% and limited to grade 1 (33%) and grade 2 (33%) with seven patients (47%) receiving tocilizumab.

CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; IV, intravenous; SC, subcutaneous; TEAE, treatment-emergent adverse event.

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Extended Data Table 2 | Effect of priming and premedication on CRS

	Elranatamab SC at recommended monotherapy dose		
	Dose escalation (RP2D) part 1 (*N* = 6)	**Priming cohort part 1.1 (*N* = 20)**	**Expansion cohort part 2A (*N* = 15)**
Priming/premedication[a]	No/No	Yes/No	Yes/Yes
Overall incidence of CRS	6 (100.0)	20 (100.0)	10 (66.7)
Grade 1	4 (66.7)	10 (50.0)	5 (33.3)
Grade 2	2 (33.3)	10 (50.0)	5 (33.3)
Median duration of CRS, days	4.0 (1.0–10.0)	3.0 (2.0–7.0)	3.0 (1.0–4.0)
Median time to onset of CRS relative to most recent dose, days	1.0 (1.0–3.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)
Supportive measures[b]			
Tocilizumab	3 (50.0)	16 (80.0)	7 (46.7)
Steroids	1 (16.7)	3 (15.0)	3 (20.0)
Oxygen	0	7 (35.0)	2 (13.3)
Vasopressor	0	0	0

Values are median (range) or *n* (%). Data cutoff was September 30, 2022. Grading of CRS based on Lee, D.W. et al. *Biol Blood Marrow Transplant* **25**, 625-638 (2019).

[a]Premedication (with acetaminophen, diphenhydramine, and dexamethasone) was given with the priming dose and first full dose.

[b]Percentage calculated based on number of patients exposed to elranatamab in each part of the study.

CRS, cytokine release syndrome; RP2D, recommended phase 2 dose; SC, subcutaneous.

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Extended Data Table 3 | Effect of priming and premedication on ICANS

	Elranatamab SC at recommended monotherapy dose		
	Dose escalation (RP2D) part 1 (*N* = 6)	**Priming cohort part 1.1 (*N* = 20)**	**Expansion cohort part 2A (*N* = 15)**
Priming/premedication[a]	No/No	Yes/No	Yes/Yes
Overall incidence of ICANS	2 (33.3)	3 (15.0)	2 (13.3)
Grade 1	2 (33.3)	1 (5.0)	1 (6.7)
Grade 2	0	2 (10.0)	1 (6.7)
Median duration of ICANS, days	4.5 (2.0–7.0)	3.0 (2.0–3.0)	1.5 (1.0–2.0)
Median time to onset of ICANS relative to most recent dose, days	1.0 (1.0–1.0)	1.0 (1.0–2.0)	2.0 (2.0–2.0)
Supportive measures[b]			
Tocilizumab	0	3 (15.0)	2 (13.3)
Steroids	1 (16.7)	1 (5.0)	1 (6.7)

Values are median (range) or *n* (%). Data cutoff was September 30, 2022. Grading of ICANS based on Lee, D.W. et al. *Biol Blood Marrow Transplant* **25**, 625-638 (2019).

[a]Premedication (with acetaminophen, diphenhydramine, and dexamethasone) was given with the priming dose and first full dose.

[b]Percentage calculated based on number of patients exposed to elranatamab in each part of the study.

ICANS, immune effector cell-associated neurotoxicity syndrome; RP2D, recommended phase 2 dose; SC, subcutaneous.

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Extended Data Table 4 | Elranatamab serum pharmacokinetic (total) parameters 1 week after a single subcutaneous dose administration

	Part 1 80 µg/kg (*N* = 2)	Part 1 130 µg/kg (*N* = 3)	Part 1 215 µg/kg (*N* = 2)	Part 1 360 µg/kg (*N* = 4)	Part 1 600 µg/kg (*N* = 5)	Part 1 1000 µg/kg (*N* = 4)	Part 1.1[a] 600/1000 µg/kg (*N* = 14)	Part 2A[a] 44/76 mg (*N* = 11)
AUC_{tau}, ng·day/ml	703, 1140	4426 (17)	435, 6090	12580 (26)	18590 (31)	25530 (36)	17700 (37)	11070 (103)
AUC_{tau} (dn), ng·day/ml/mg	73.2, 270	393.8 (40)	298, 597	431.1 (30)	337.3 (30)	414.5 (35)	421.3 (47)	251.4 (103)
C_{max}, ng/ml	172, 206	829.3 (19)	979, 1140	2568 (42)	3857 (13)	4834 (25)	4084 (37)	2682 (99)
C_{max} (dn), ng/ml/mg	17.9, 49.0	73.86 (51)	67.1, 112	87.88 (39)	69.95 (13)	78.44 (27)	97.28 (46)	60.95 (99)
T_{max}, day	3.00, 6.89	2.93 (2.93–7.90)	7.00, 7.93	6.94 (4.98–6.98)	7.02 (6.72–7.12)	6.91 (4.92–7.08)	6.98 (6.93–6.99)	6.99 (6.98–7.00)

Values are geometric mean (geometric % coefficient of variation) for all parameters except median (IQR) for T_{max}. Data cutoff was September 30, 2022. *N* represents the number of participants with sufficient information to estimate at least one PK parameter for AUC_{tau}, AUC_{tau} (dn), C_{max}, C_{max} (dn), or T_{max}. Individual values are listed when there are less than three evaluable measurements. Tau is 1 week since the first dose.

[a]Participants in Part 1.1 and Part 2A received a priming dose of 600 µg/kg (or equivalent fixed dose of 44 mg) for the first dose.

AUC_{tau}, area under the plasma concentration-time curve from time zero to the end of the dosing interval; C_{max}, maximum observed plasma concentration; dn, dose normalized; IQR, interquartile range; PK, pharmacokinetic; T_{max}, time of the maximum observed plasma concentration.

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Extended Data Table 5 | Efficacy endpoints reported in RRMM for currently approved BCMA-targeted immunotherapies

	Teclistamab (MajesTEC-1)[1]	Ide-cel (KarMMa)[2]	Cilta-cel (CARTITUDE-1)[3]
ORR, %	63.0 (104/165)	67.1[a] (94/140)	83.2[a] (94/113)
Median DOR, months	18.4 (14.9–NE)	10.7 (9.0–11.3)	NR (15.9–NE)
Median PFS, months	11.3 (8.8–17.1)	8.8 (5.6–11.6)	NR (16.8–NE)
Median OS, months	18.3 (15.1–NE)	19.4 (18.2–NE)	Not reported
Median follow-up, months	14.1 (Range 0.3–24.4)	13.3 (Range 0.2–21.2)	12.4 (IQR 10.6–15.2)

Values are median (95% CI) for all parameters except median (range or IQR) for follow-up, and % (*n*/N) for ORR. *n* represents the number of participants achieving ORR and *N* represents the total number of evaluable participants. References: 1. Moreau, P. et al. *N Engl J Med* **387**, 495–505 (2022); 2. Munshi, N.C. et al. *N Engl J Med* **384**, 705–716 (2021); 3. Berdeja, J.G. et al. *Lancet* **398**, 314–324 (2021).

[a]Among patients who underwent leukapheresis.

BCMA, B-cell maturation antigen; CI, confidence interval; cilta-cel, ciltacabtagene autoleucel; DOR, duration of response; ide-cel, idecabtagene vicleucel; IQR, interquartile range; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed or refractory multiple myeloma

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Corresponding author(s): Nizar J. Bahlis

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Oracle Clinical Remote Data Capture (OCRDC) 5.4.0
Data analysis	SAS version 9.4.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The URL in the current statement includes the most up-to-date information, including time frame, restrictions contact details, etc., with respect to data request. The statement is: "Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information. The protocol and statistical analysis plan for MagnetisMM-1 have been uploaded to clinicaltrial.gov."

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Information on sex was obtained for all study participants and is detailed in Table 1. 26 (47.3) participants were female, and 29 (52.7%) participants were male. No information about gender was collected. No analysis was performed based on sex since this was not the focus of this study.
Reporting on race, ethnicity, or other socially relevant groupings	Information on race was obtained for all study participants and is detailed in Table 1. No analysis was performed based on race.
Population characteristics	No covariate analysis was conducted. The baseline characteristics of study participants are detailed in Table 1.
Recruitment	Patients were recruited by participating investigators. Investigators obtained written informed consent from each patient before any study-specific activity was performed. A total of 14 investigative centers (11 in the USA, 3 in Canada) enrolled patients from November 2017 through April 2021. Due to the geographical distribution of the study centers, participants may not represent the global general population. No other bias emerging from recruitment is expected.
Ethics oversight	This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice. Informed consent documents and patient recruitment materials were compliant with International Conference on Harmonization Good Clinical Practice, local regulatory requirements, and legal requirements, including applicable privacy laws. The study protocol and relevant documents were approved by an independent institutional review board or ethics committee at each investigative center. Patient safety was monitored jointly by investigators and a safety assessment committee established by the sponsor.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	This phase 1 trial utilized modified toxicity probability interval procedure for patient allocation and hence the sample size was not pre-determined. This is typical for phase 1 dose-finding clinical trials.
Data exclusions	Data for patients who received intravenous therapy and subcutaneous therapy at sub-efficacious dose levels not associated with International Myeloma Working Group confirmed responses of partial response or better were excluded from the analysis presented in the article.
Replication	Replication is not applicable for human clinical trial as each patient is individual and inherently different.
Randomization	This was a non-randomized phase 1 study. Data collection was prospective without controling for covariates.
Blinding	This was an open-label study. Participants were not randomized.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT03269136
Study protocol	Information can be accessed at : https://www.clinicaltrials.gov/ct2/show/NCT03269136 or by reviewing the study protocol in the Supporting Information.
Data collection	Patients were enrolled from 14 investigative centers from November 2017 through April 2021; the data cutoff was September 30, 2022.
Outcomes	As defined in the protocol (accessible via URL above), the primary safety endpoint was the number of dose-limiting toxicities; the primary efficacy endpoints were objective response rate and duration of response for patients treated at efficacious doses, with response assessed according to International Myeloma Working Group (IMWG) criteria. Secondary endpoints included adverse events, laboratory abnormalities, objective response rate, time to response, complete response rate, duration of response, progression-free survival, overall survival, rate of minimal residual disease negativity, pharmacokinetic parameters, immunogenicity, and levels of serum cytokines. Primary and secondary endpoints were predefined in the protocol before the trial began enrollment. They were assessed as per description in the methods section, including the following: "The dose-limiting toxicity observation period was through the end of the first treatment cycle for each patient in Part 1. Treatment-emergent adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Both cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome were defined and graded according to American Society for Transplantation and Cellular Therapy consensus criteria. Tumor response and disease progression were assessed according to IMWG response criteria, and objective response rate was calculated based on confirmed responses reported by investigators. Minimal residual disease at a sensitivity of 1×10–5 was centrally assessed by next-generation sequencing (clonoSEQ®, Adaptive Biotechnologies, Seattle, WA, USA) according to IMWG response criteria. Pharmacokinetics, cytokines, lymphocyte subsets, and serum levels of soluble B-cell maturation antigen were analyzed over time."