



CORRESPONDENCE

CM313 Monotherapy in Patients With Relapsed/Refractory Multiple Myeloma or Marginal Zone Lymphoma: A Multicenter, Phase 1 Dose-Escalation and Dose-Expansion Trial

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To the Editor,

Multiple myeloma (MM) accounts for approximately one-tenth of all hematological malignancies. Although immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) have significantly prolonged survival of MM patients, relapses are almost inevitable [1]. Patients refractory to IMiDs and PIs have a poor prognosis, highlighting the urgency to develop new agents with target specificity in patients with relapsed/refractory MM (RRMM). CD38 is a type 2 transmembrane glycoprotein highly expressed in hematological malignancies and low in normal tissues, permitting CD38-targeting antibody a novel therapeutic option for RRMM. Currently, two anti-CD38 monoclonal antibodies, daratumumab and isatuximab, have been approved for the treatment of RRMM [2–4].

CM313 is a novel humanized monoclonal antibody with a unique complementarity-determining region sequence that facilitates its high affinity to a spectrum of CD38-positive cells. Preclinical studies showed its comparable *in vitro* killing activities in target cells and anti-tumor activities with daratumumab,

without obvious off-target toxicity [5]. CM313 also demonstrated encouraging efficacy and favorable safety in patients with immune thrombocytopenia [6]. Here, we report the first-in-human phase 1 trial of CM313 monotherapy in patients with RRMM and marginal zone lymphoma (MZL).

This was a multicenter, open-label phase 1 trial consisting of a dose-escalation phase and a dose-expansion phase (NCT04818372). Eligible RRMM patients had a confirmed diagnosis of MM based on the International Myeloma Working Group guidelines, measurable disease, an Eastern Cooperative Oncology Group performance-status score of ≤ 2 points, and prior treatment with IMiDs and PIs. Key exclusion criteria were primary refractory MM, diagnosis of amyloidosis, plasma-cell leukemia, or polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS) syndrome, confirmed central nervous system metastases, and prior therapy with anti-CD38 monoclonal antibodies. Detailed eligibility criteria for RRMM and MZL patients are presented in the [Supporting Information](#). Patients in the dose-escalation phase received 9 escalating doses of CM313 intravenously (0.006, 0.06, 0.3, 1.0, 2.0,

4.0, 8.0, 16, and 24 mg/kg) once in a 21-day observation period for dose-limiting toxicities (DLTs), then once weekly (QW) for the next 7 doses, then every 2 weeks (Q2W) for 8 doses, and then every 4 weeks (Q4W) onwards until disease progression or unacceptable toxicities. In the dose-expansion phase, CM313 was administered intravenously at doses of 4.0 and 16 mg/kg QW for 8 doses, then Q2W for 8 doses, and then Q4W thereafter until disease progression or unacceptable toxicities (Figure S1A).

Primary endpoints were safety and tolerability in the dose-escalation phase and overall response rate (ORR) in the dose-expansion phase. Secondary endpoints included clinical benefit rate (CBR), time to response, duration of response (DOR), progression-free survival (PFS), overall survival (OS), pharmacokinetics, pharmacodynamics, and immunogenicity. The study design and procedures are detailed in the [Supporting Information](#).

Between April 15, 2021 and August 3, 2023, 41 patients with RRMM and three with MZL were enrolled in this trial. As of the end of the study (April 3, 2024), 6 patients remained on treatment and 38 had discontinued treatment due to disease progression ($n = 31$ [70.5%]), subject's decision ($n = 4$ [9.1%]), or investigator's decision ($n = 3$ [6.8%]) (Figure S1B). In RRMM patients, median time since diagnosis was 4.4 years (range 0.9–10.3) and patients had received a median of 3 (range 2–10) lines of prior therapies. All 41 RRMM patients had previously received PIs and IMiDs (Table S1). Baseline demographic and disease characteristics of MZL patients are presented in Table S2.

No DLTs were reported up to 24 mg/kg and the maximum tolerated dose was not reached. Thirty-two infusion-related reactions (IRRs) were reported in 59.1% (26/44) of patients and were of grade 1 or 2, except for one patient with RRMM in the 1.0 mg/kg cohort who experienced a grade 3 reaction during the first infusion. IRRs occurred in 59.1% (26/44) of patients during the first infusion and in 12.5% (5/40) of patients during subsequent infusions (Figure S2). All IRRs resolved either spontaneously or with treatment, with a median duration of 1.5 h (range 0.0–151.4). The most common treatment-emergent adverse events (TEAEs), excluding IRRs, were white blood cell count decreased (47.7%) and lymphocyte count decreased (43.2%) (Table S3). Twenty-five (56.8%) patients reported grade ≥ 3 TEAEs and 19 (43.2%) patients reported grade ≥ 3 drug-related TEAEs. Ten (22.7%) patients reported serious adverse events (SAEs) and 6 (13.6%) patients reported drug-related SAEs. There were no TEAEs leading to permanent treatment discontinuation. One patient in the 16 mg/kg cohort experienced one TEAE leading to death (respiratory failure) which was deemed unrelated to the study drug. Grade 2 COVID-19 was reported in this patient 3 days before he died.

The median follow-up was 19.4 months (range 3.6–36.5) for all enrolled patients and 19.3 months (range 4.5–36.5) for RRMM patients. A waterfall plot of percent changes in paraprotein is shown in Figure 1A. The ORR was 36.6% (15/41, 95% confidence interval [CI] 22.1%–53.1%) in all RRMM patients and 44.4% (8/18, 95% CI 21.5%–69.2%) in the 16 mg/kg dose cohort. The CBR was 46.3% (19/41, 95% CI 30.7%–62.6%) in all RRMM patients and 50.0% (9/18, 95% CI 26.0%–74.0%) in the 16 mg/kg dose cohort (Table S4). In patients who had a response to

treatment, the median time to response was 0.9 months (range 0.5–2.8) and DOR was 16.4 months (95% CI 6.6–NR). In patients responding to 16 mg/kg of CM313, the median time to response was 1.3 months (range 0.9–2.8) and the median DOR was 16.4 months (range 3.7–NR) (Figure S3 and Table S4).

The median PFS was 4.3 months (95% CI 2.3–8.5) in all RRMM patients and 4.6 months (95% CI 2.0–17.9) in the 16 mg/kg cohort (Figure 1B and Table S4). The median OS was not reached (95% CI 19.5–NR). The 12-month and 24-month OS rates were 80.5% (95% CI 64.8%–89.7%) and 60.5% (95% CI 41.6%–75.0%) in all RRMM patients, respectively, and 88.9% (95% CI 62.4%–97.1%) and 67.3% (95% CI 36.6%–85.6%) in the 16 mg/kg cohort, respectively (Figure 1C and Table S4). Treatment responses and survival of MZL patients are presented in Table S5.

CM313 exposure, as measured by the maximum observed serum concentration and area under the concentration-time curve, increased in a greater than dose-proportional manner (Figure S4 and Table S6). The elimination of CM313 appeared to be nonlinear and time-varying. Mean elimination half-life increased and clearance decreased with increasing doses and multiple doses (Table S6). Receptor occupancy (CD3+ T cell, CD14+ monocyte, and CD19+ B cell) reached 60%–100% at 2 h after a single dose and maintained high during the treatment (Figure S5). Peripheral blood NK cell (total and CD38+) counts of RRMM patients decreased by 80%–100% compared to baseline in all dose groups in the dose-escalation and dose-expansion phases (Figure S6). All patients in this trial were negative for treatment-related anti-drug antibody.

This first-in-human study showed that CM313 monotherapy was well tolerated and displayed encouraging efficacy in patients with RRMM who had a median of three lines of prior therapy. IRRs and other TEAEs were generally tolerable and manageable. RRMM patients achieved rapid (median time to response, 0.9 months), deep (24.4% with VGPR or better), and durable (median DOR, 16.4 months) responses with CM313 monotherapy. Median PFS was 4.3 months and median OS was not reached, with a 12-month OS rate of 80.5%.

CM313 showed favorable safety and tolerability. IRRs were reported in 59.1% of all enrolled patients and were manageable through peri-infusion medications or by lowering the infusion rate and other symptomatic treatment in this study. The most common TEAEs excluding IRRs were hematological, consistent with daratumumab and isatuximab [3, 4]. SAEs were reported in 22.7% of all enrolled patients and in 25.0% of the 16 mg/kg cohort in this study, compared to 33%–48.9% with daratumumab 16 mg/kg [2, 3] and 43% with isatuximab 10–20 mg/kg [4]. No TEAEs leading to permanently treatment discontinuation were reported, indicating that CM313 was tolerated in RRMM patients. No new safety signal was identified.

With an innovative complementarity-determining region molecular structure, CM313 may differ in reorganization and interaction with epitopes compared to other anti-CD38 monoclonal antibodies. Preclinical studies showed comparable anti-tumor activity of CM313 with daratumumab [5]. In this study, ORR was 36.6% in all RRMM patients and 44.4% in the 16 mg/kg cohort, comparable to the ORR in RRMM patients receiving

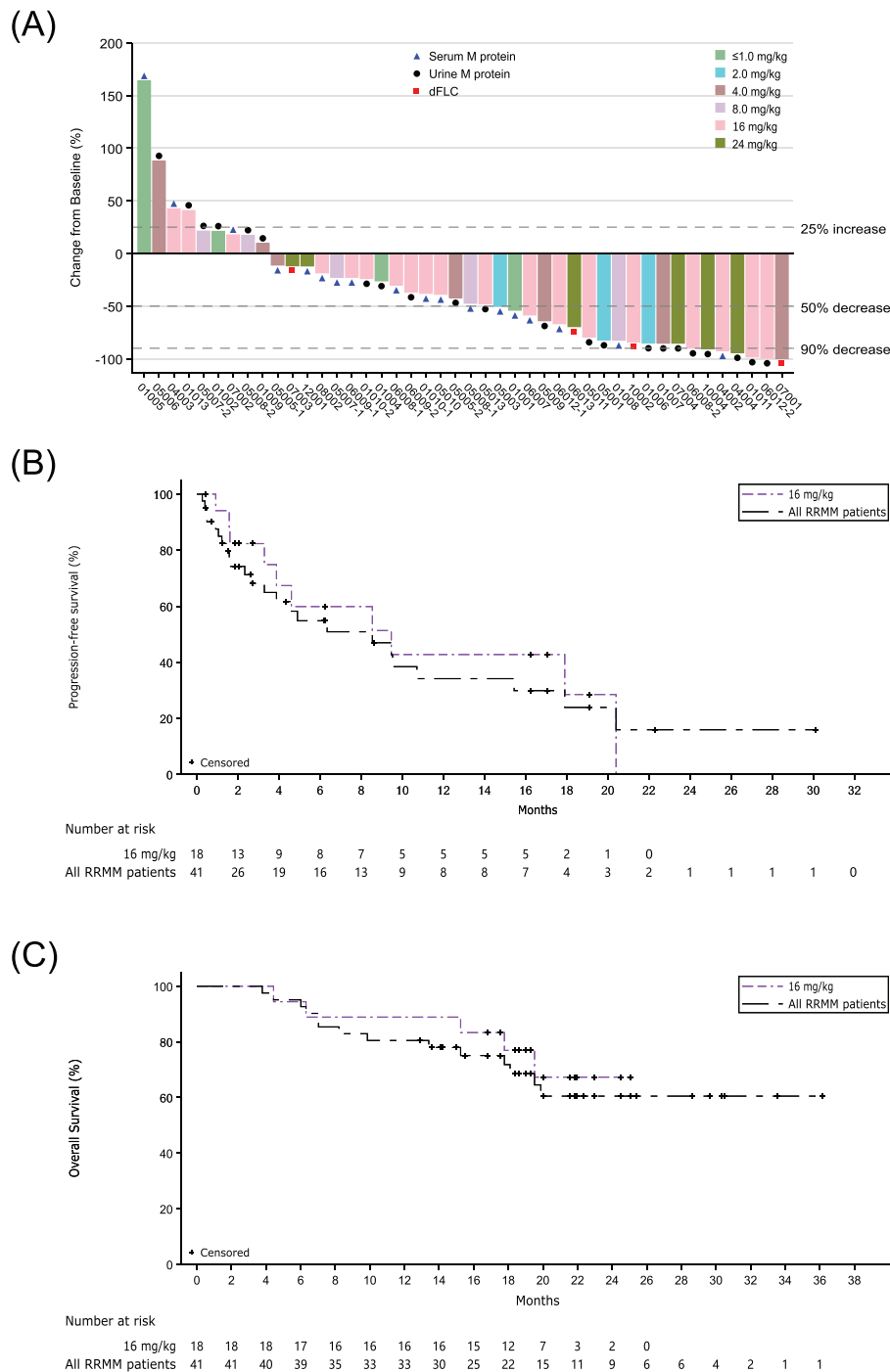


FIGURE 1 | Treatment response and survival in RRMM patients. (A) The maximum percent change from baseline in paraprotein. ≤ 1.0 mg/kg cohorts included 0.006, 0.06, 0.3, and 1.0 mg/kg cohorts. (B) Progression-free survival. (C) Overall survival. dFLC, differences in serum free light chains; RRMM, relapsed/refractory multiple myeloma.

daratumumab 16 kg/mg (36%–42.6%) [2, 3] and isatuximab 10 kg/mg or higher (23.8%) [4]. Median DOR was 16.4 months in the present study, similar to 18.9 months obtained in Chinese RRMM patients receiving daratumumab 16 kg/mg [3].

Median PFS in this study was 4.3 months for all RRMM patients and 4.6 months for the 16 kg/mg cohort, comparable to daratumumab and isatuximab in the aforementioned phase 1–2 trials (2.9–6.7 months) [2–4]. The median OS in this study was not reached; the 12-month OS rate were 80.5% in the total

population and 88.9% in the 16 kg/mg subgroup, similar to those of daratumumab and isatuximab monotherapy in the above trials (69.8%–78.1%) [2, 3]. Further follow-up will provide mature OS data.

In conclusion, CM313 monotherapy demonstrated a manageable safety profile and promising clinical efficacy in patients with RRMM or MZL. A multi-center phase 1/2 study is underway to evaluate the efficacy and safety of CM313 subcutaneous injections in RRMM patients (NCT06126237).

Author Contributions

All authors report substantial contributions to the conception and design of the studies, acquisition of data, or the analysis or interpretation of data; have critically reviewed the manuscript; approved the final version; agree with all content; and agree to be accountable for all aspects of the work.

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Consent

All participants signed written informed consents before enrollment. The consent forms were approved by the ethics committee at each trial site.

Conflicts of Interest

Yanrong Wang and Ling Li are employees of KeyMed Biosciences (Chengdu) Co., Ltd. All other authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.