Original Study

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Daratumumab With Cetrelimab, an Anti–PD-1 Monoclonal Antibody, in Relapsed/Refractory Multiple Myeloma

Yael C. Cohen,[1] Albert Oriol,[2] Ka Lung Wu,[3] Noa Lavi,[4] Philip Vlummens,[5] Carolyn Jackson,[6] Wendy Garvin,[6] Robin Carson,[7] Wendy Crist,[7] Jiayu Fu,[7] Huaibao Feng,[7] Hong Xie,[7] Jordan Schecter,[6] Jesús San-Miguel,[8] Sagar Lonial[9]

Abstract

Patients with relapsed or refractory multiple myeloma have an immunosuppressive state with upregulation of programmed death receptor-1 on immune effector cells. Treatment with daratumumab plus cetrelimab, which targets the programmed death receptor-1, was evaluated in 9 patients with relapsed or refractory multiple myeloma. No new safety concerns were identified for the combination. The potential clinical benefit of daratumumab plus cetrelimab remains uncertain.

Background: Daratumumab is approved for relapsed or refractory multiple myeloma (RRMM) as monotherapy or in combination regimens. We evaluated daratumumab plus cetrelimab, a programmed death receptor-1 inhibitor, in RRMM. **Patients and Methods:** This open-label, multiphase study enrolled adults with RRMM with ≥ 3 prior lines of therapy. Part 1 was a safety run-in phase examining dose-limiting toxicities of daratumumab (16 mg/kg intravenously weekly for cycles 1-2, biweekly for cycles 3-6, and monthly thereafter) plus cetrelimab (240 mg intravenously biweekly, all cycles). In Parts 2 and 3, patients were to be randomized to daratumumab with or without cetrelimab (same schedule as Part 1). Endpoints included safety, overall response rate, pharmacokinetics, and biomarker analyses. **Results:** Nine patients received daratumumab plus cetrelimab in the safety run-in, and 1 received daratumumab in Part 2 before administrative study termination following a data monitoring committee's global recommendation to stop any trial including daratumumab combined with inhibitors of programmed death receptor-1 or its ligand (programmed death-ligand 1). The median follow-up times were 6.7 months (safety run-in) and 0.3 months (Part 2). No dose-limiting toxicities occurred. All 10 patients had ≥ 1 treatment-emergent adverse event; 7 patients had grade 3 to 4 treatment-emergent adverse events, and none led to treatment discontinuation or death. In the safety run-in, 7 (77.7%) patients had ≥ 1 infusion-related reaction (most grade 1-2), and 1 had a grade 2 immune-mediated reaction. Among safety run-in patients, the overall response rate was 44.4%. **Conclusions:** No new safety concerns were identified for daratumumab plus cetrelimab in RRMM. The short study duration and small population limit complete analysis of this combination.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 21, No. 1, 46-54 © 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: CD38, Efficacy, Programmed death receptor-1, RRMM, Safety

[1]Tel-Aviv Sourasky (Ichilov) Medical Center, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[2]Institut Català d'Oncologia i Institut Josep Carreras, Hospital Germans Trias I Pujol, Badalona, Barcelona, Spain
[3]Department of Hematology, ZNA Stuivenberg Lange Beeldekensstraat, Antwerpen, Belgium
[4]Department of Hematology and Bone Marrow Transplantation, Rambam Medical Center, Haifa, Israel
[5]Department of Clinical Hematology, UZ Gent - Department of Clinical Hematology, Gent, Belgium
[6]Janssen Research & Development, LLC, Raritan, NJ
[7]Janssen Research & Development, LLC, Spring House, PA
[8]Clínica Universidad de Navarra-CIMA, IDISNA, CIBERONC, Pamplona, Navarra, Spain
[9]Winship Cancer Institute, Emory University, Atlanta, GA

Submitted: Dec 13, 2019; Revised: May 15, 2020; Accepted: Aug 11, 2020; Epub: Aug 22, 2020

Address for correspondence: Yael C. Cohen, MD, Tel-Aviv Sourasky (Ichilov) Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Weizmann St 6, Tel Aviv, Israel
E-mail contact: yaelcoh@tlvmc.gov.il

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https://doi.org/10.1016/j.clml.2020.08.008

Introduction

Survival has improved dramatically over the past 20 years for patients with multiple myeloma (MM),[1] owing in part to novel treatment options including proteasome inhibitors (PIs), immunomodulatory agents (IMiDs), histone deacetylase inhibitors, and monoclonal antibodies. However, MM remains incurable, and most patients eventually experience progressive disease. The estimated 5-year survival rate for patients with newly diagnosed MM (NDMM) is 52%,[1] whereas patients with relapsed or refractory multiple myeloma (RRMM) have poorer outcomes. Real-world studies report median progression-free survival (PFS) times of 5 to 13 months[2,3] and median overall survival (OS) of approximately 20 to 32 months among patients with RRMM that failed multiple lines of therapy.[3,4] Thus, there is an unmet need for more effective therapies, particularly among patients with RRMM.

Daratumumab is a human IgG1κ anti-CD38 monoclonal antibody approved as monotherapy for the treatment of RRMM and as combination therapy for RRMM and NDMM.[5] Daratumumab has a direct on-tumor[6-9] and immunomodulatory mechanism of action.[10-12] Daratumumab-induced on-tumor activity occurs through several CD38 immune-mediated actions (complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis), apoptosis, and modulation of CD38 enzymatic activity.[6-9] Daratumumab induces an immunomodulatory effect that minimizes the immune-suppressive functions of $CD38^+$ myeloid-derived tumor suppressor cells (MDSCs), regulatory T cells (T_{regs}), and regulatory B cells and increases T-cell clonality.[10-12]

In patients with MM, the immune checkpoint protein programmed death receptor-1 (PD-1) is upregulated on effector T cells and natural killer (NK) cells, and the programmed death-ligand 1 (PD-L1) is expressed on malignant plasma cells.[13,14] Overexpression of PD-1 or PD-L1 creates an immunosuppressive microenvironment associated with disease progression.[13-15] For these reasons, the role of PD-(L)1 in MM disease progression is of interest, as is the therapeutic potential of PD-(L)1 blockade. Cetrelimab is a fully human monoclonal IgG4κ anti–PD-1 antibody. In a phase I/II study of cetrelimab in 192 patients with advanced or refractory solid tumors, cetrelimab was well tolerated and had promising antitumor activity, with 2 patients achieving a complete response (CR), 22 achieving a partial response (PR), and one-half achieving stable disease (SD) or better.[16] Other antibodies directed against PD-1 have shown anti-myeloma activity in early clinical results in RRMM when combined with IMiDs,[17,18] suggesting that cetrelimab plus the direct on-tumor and immunomodulatory action of daratumumab may have therapeutic potential among patients with MM.

The main objectives of this study were to assess the safety, efficacy, pharmacokinetics (PK), and blood biomarker changes associated with daratumumab with or without cetrelimab among patients with RRMM.

Materials and Methods

Study Design

This was an open-label, multicenter, multiple-phase study to assess the safety and efficacy of daratumumab with or without cetrelimab among patients with RRMM. The study included a screening phase (28 days before enrollment) followed by 3 treatment phases (Parts 1, 2, and 3), and a follow-up phase. Part 1 comprised the safety run-in phase to evaluate safety and tolerability based on dose-limiting toxicity (DLT) in cycle 1. In Parts 2 and 3, patients were to be randomized 1:1 to daratumumab or daratumumab plus cetrelimab. The study protocol was reviewed and approved by a local independent ethics committee or institutional review board at each study site. This study was conducted in accordance with the ethical principles in the Declaration of Helsinki and was consistent with good clinical practices and applicable regulatory requirements. Written consent to participate in the study was obtained before any study-related activity. The study was registered with ClinicalTrials.gov (NCT03357952); EudraCT Number 2017-002611-34.

Patients

Adults ($\geq$ 18 years of age) with documented, measurable RRMM and who had received at least 3 prior lines of therapy (including a PI and an IMiD) or were refractory to both a PI and an IMiD were included. Patients also had evidence of PR or better to at least 1 prior treatment based on investigator's determination of response by the International Myeloma Working Group criteria[19-21]; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; hemoglobin $\geq$ 7.5 g/dL; absolute neutrophil count $\geq 1.0 \times 10^9$/L; platelet count $\geq 75 \times 10^9$/L ($\geq 50 \times 10^9$/L if $\geq$ 50% of the bone marrow is infiltrated with MM cells); aspartate aminotransferase and alanine aminotransferase each $\leq 2.5 \times$ the upper limit of normal; total bilirubin $\leq 2.0 \times$ the upper limit of normal; estimated creatinine clearance $\geq$ 30 mL/min; and corrected serum calcium $\leq$ 14 mg/dL (or free ionized calcium $\leq$ 6.5 mg/dL). Patients who had received prior daratumumab treatment were excluded. Additional eligibility criteria are listed in the Supplementary Appendix (in the online version).

Treatments

The safety run-in phase had a single treatment arm in which patients received daratumumab (16 mg/kg intravenously [IV] weekly for the first 2 cycles [on days 1, 8, 15, and 22; all cycles were 28 days], followed by every other week in cycles 3 to 6 [on days 1 and 15], and then once every 4 weeks on day 1 of each cycle thereafter) with cetrelimab (240 mg IV on day 2 and day 15 of cycle 1, and then on day 1 and day 15 of all cycles thereafter). Cetrelimab was given after daratumumab infusion, when applicable. Details on pre- and post-infusion medications are included in the Supplementary Appendix (in the online version).

In Parts 2 and 3, patients were to receive daratumumab plus cetrelimab or daratumumab alone with the same dosing regimens as in Part 1. Daratumumab and cetrelimab toxicities were managed by dose delay. Study treatment continued until confirmed disease progression, unacceptable toxicity, or if other discontinuation criteria were met. Patients who discontinued cetrelimab were given the option to continue on daratumumab monotherapy until meeting the discontinuation criteria described above.

During the safety run-in phase, if $<$ 2 patients of the first 6 DLT-evaluable patients experienced a DLT during the first treatment cycle, the selected dose and dose regimens for daratumumab

plus cetrelimab were considered tolerable, and the study could proceed to Part 2 after approval from the safety evaluation team.

Endpoints and Assessments

The primary objective of the safety run-in (Part 1) was to assess the safety of daratumumab plus cetrelimab by monitoring the incidence of adverse events (AEs), including DLTs (primary endpoint). AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03. The DLT evaluation period was 28 days starting from the day of the first dose of study treatment.

DLTs included any of the following events: aspartate aminotransferase or alanine aminotransferase toxicity (grade $\geq$ 3 lasting $\geq$ 7 days after treatment with corticosteroids, grade 4, or any meeting Hy's Law criteria); laboratory abnormality (grade 3 lasting $\geq$ 7 days despite best supportive care [BSC] or grade 4); any grade $\geq$ 3 event lasting $\geq$ 7 days despite BSC (or any grade 4 event, except any grade $\geq$ 3 rash that was asymptomatic/mildly symptomatic and adequately managed or resolved to asymptomatic/grade $\leq$ 2 within 7 days of supportive therapy); any grade 4 infusion-related reaction (IRR) occurring within 24 hours of study drug infusion; neutropenia (grade 4 lasting > 7 days despite BSC, or grade 3 febrile neutropenia, or sepsis); thrombocytopenia (grade $\geq$ 3 with clinically significant bleeding or grade 4 lasting > 7 days despite BSC); anemia (grade 4 lasting > 7 days despite BSC); or any grade 5 event.

Safety was assessed by the incidence and severity of AEs, laboratory test results, electrocardiograms, vital sign measurements, physical examination findings, and ECOG performance status score. The safety analysis set included all patients who received $\geq$ 1 dose of study drug. AE monitoring was continuous starting from the date of informed consent until 30 days after the last dose of study drug, until the start of subsequent anticancer therapy, or study withdrawal. Drug-related serious AEs (SAEs) were monitored in the follow-up period (8 weeks after the last dose of study drug and every 12 weeks thereafter).

In Parts 1 and 2, efficacy was assessed by overall response rate (ORR), defined as the proportion of patients with PR or better. Disease evaluations were performed every 28 days ($\pm$3 days) by a central laboratory until disease progression and assessed according to International Myeloma Working Group criteria.[19-21]

PK analyses were performed for patients who received $\geq$ 1 dose of daratumumab or cetrelimab and who had $\geq$ 1 post-infusion sample. Samples were to be collected for measurement of serum concentration of, and possible antibodies against, daratumumab and cetrelimab before and after infusions on day 1 of cycles 1, 2, 3, 5, 7, 12, 16 (cetrelimab only for this cycle), 24, and every 12 cycles thereafter, at the end of treatment visit, and at the follow-up visit. Maximum observed concentration (C_{max}), minimum observed concentration (C_{trough}), and coefficient of variation were measured. All concentrations below the lowest quantifiable concentration were treated as zero.

Biomarker evaluation was an exploratory endpoint conducted on samples taken during cycle 1 (day 1, 8, and 15), cycle 2 (day 1 and 15), on day 1 of cycle 4, and at disease progression. Immunophenotyping was performed on whole blood by flow cytometry. Values and changes from baseline at each scheduled visit for absolute counts (cells/μL) and percentage of total NK cells, $CD8^+$ T cells, and B cells in peripheral blood were plotted or summarized. Similar analyses were performed for total and $CD38^+$ MDSCs, and total and $CD38^+$ T_{regs}.

Statistical Analyses

Safety data were provided as the percentage of patients who experienced $\geq$ 1 AE by treatment group, and comparisons between treatment groups were to be conducted as appropriate. For response rates, the number and percentage of patients in each response category were tabulated, and the ORRs were to be tabulated and provided with 2-sided 95% confidence intervals for each treatment group. For time-to-event endpoints (eg, duration of response, PFS, and OS), Kaplan-Meier estimates were to be provided for each treatment group; treatment comparisons for PFS and OS were made by the log-rank test. Cox regression analyses were to provide the hazard ratio estimates and the 95% confidence intervals to measure treatment effect. PK and immunogenicity data were to be summarized using descriptive analyses. Biomarker analyses were to be stratified by clinical covariates or molecular subgroups and analyzed by the appropriate statistical method depending on the endpoint (parametric/non-parametric, univariate/multivariate, analysis of variance, or survival analysis).

Results

On May 25, 2018 (186 days after enrollment of the first patient), this study was terminated for administrative reasons after 10 patients had enrolled. Termination of this study was a conservative measure based on results from the phase Ib/II LUC2001 study (ClinicalTrials.gov Identifier, NCT03023423). LUC2001 evaluated the efficacy and safety of a PD-L1 inhibitor, atezolizumab, with or without daratumumab among patients with previously treated advanced or metastatic non–small-cell lung cancer (NSCLC). The decision to discontinue LUC2001 occurred at a planned review by the data monitoring committee and was based on a lack of observed improved efficacy among patients who received the combination of daratumumab plus atezolizumab for NSCLC in that study. The ORR was lower in the daratumumab plus atezolizumab group in LUC2001, but other efficacy endpoints were similar between treatment groups. Additionally, although there was an imbalance of deaths in the daratumumab plus atezolizumab group, these events were not attributed to increased drug-related toxicity of the combination regimen. Regardless, in response to these data, the study sponsor stopped further enrollment on all studies with PD-1 or PD-L1 inhibitors combined with daratumumab, including the present study.[22]

Patients

Between November 20, 2017, and September 24, 2018 (data cutoff), 10 patients were enrolled in the study. In the safety run-in phase, 9 patients received daratumumab plus cetrelimab. In Part 2 of the study, 1 patient was randomized to receive daratumumab alone.

Of the 9 patients in the safety run-in phase, 5 (55.6%) were male, and 8 (88.9%) were white; the median age was 64.0 years (range, 44-79 years) (Table 1). Six (66.7%) of 9 patients had a baseline ECOG performance status score of 0, and 3 (33.3%) had a score of 1. Four (44.4%) patients had measurable disease confined

Table 1 Patient Demographic and Disease Characteristics

Characteristic	Safety Run-in (Daratumumab + Cetrelimab) (n = 9)
Median (range) age, y	64.0 (44-79)
Male, n (%)	5 (55.6)
Race, n (%)	
White	8 (88.9)
Black or African American	1 (11.1)
Ethnicity, n (%)	
Not Hispanic/Latino	9 (100.0)
ECOG performance status, n (%)	
0	6 (66.7)
1	3 (33.0)
Type of myeloma, n (%)[a]	
IgG	3 (33.3)
IgA	2 (22.2)
IgM	1 (11.1)
Light chain (Kappa)	1 (11.1)
Negative immunofixation	2 (22.2)
ISS disease stage, n (%)	
I	5 (55.6)
II	3 (33.3)
III	1 (11.1)
Cytogenetic profile, n (%)	
Standard risk	9 (100.0)
Number of lines of prior therapy	
Median (range)	3.0 (2-5)
Patients with $\leq$ 3 prior lines, n (%)	5 (55.6)
Patients with $>$ 3 prior lines, n (%)	4 (44.4)
Median (range) time from diagnosis to first dose, mo	50.6 (16.4-287.0)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; Ig = immunoglobulin; ISS = International Staging System.
[a]By immunofixation or serum free light chain assay.

to serum only, with IgG being the most common immunoglobulin type. All had standard cytogenetic risk. The median time from initial diagnosis to the first dose of study treatment was 50.6 months (range, 16.4-287.0 months). All 9 patients were previously treated with PIs plus an IMiD, dexamethasone, and alkylating agents; 2 were previously treated with anthracyclines. Eight (88.9%) patients had previously received autologous stem cell transplant and 2 (22.2%) received prior radiotherapy. The patient in Part 2 was a 43-year-old white male with a baseline ECOG performance status score of 0 and standard cytogenetic risk (see Supplemental Table 1 in the online version).

All 10 patients enrolled received $\geq$ 1 dose of any study drug. All 9 patients in the safety run-in cohort discontinued participation in the study owing to administrative closure and were given the option to receive daratumumab monotherapy. At the time of data cutoff, 5 (55.6%) patients in the safety run-in phase had discontinued treatment owing to progressive disease, and 4 (44.4%) were continuing on daratumumab monotherapy. The median follow-up in the safety run-in phase was 6.7 months (range, 4.2-7.0 months) at the time when all 9 patients in the safety run-in phase were withdrawn from the study. The patient who enrolled in Part 2 withdrew consent 7 days after receiving the first daratumumab dose, with a follow-up time of 0.3 months. Figure 1 shows a summary of patient disposition and treatment allocation at study termination.

Study Drug Exposure

In the safety run-in phase, the median number of daratumumab infusions was 16.0 (range, 3-18), and the median number of cetrelimab infusions was 7.0 (range, 2-13). The median number of treatment cycles was 7.0 (range, 1-8) and the median duration of treatment was 5.7 months (range, 0.5-7.0 months). The median relative dose intensity was 100% (range, 74.9%-102.7%) for daratumumab and 88.9% (range, 75.0%-100%) for cetrelimab.

Efficacy

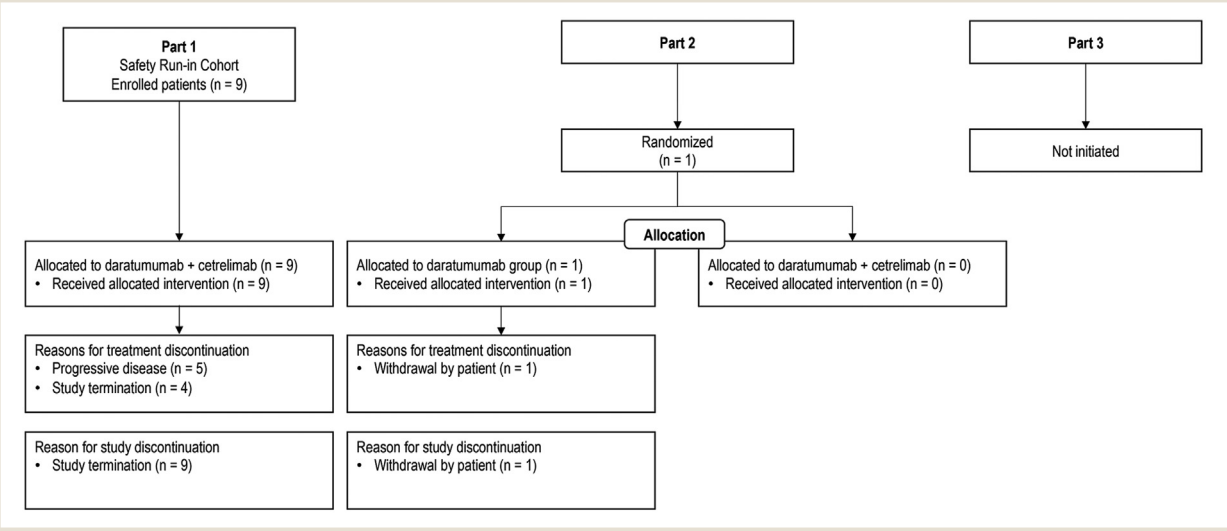
Among the 9 evaluable patients (all safety run-in), the ORR was 44.4%; 3 patients had a best response of very good partial response (VGPR), and 1 had a PR. Time to response among the 4 patients with VGPR or PR ranged from 30 to 57 days. There were no CRs. Of the remaining patients, the best responses were SD (n = 4) and PD (n = 1). There were 4 events of disease progression occurring at 1.0, 3.9, 5.1, and 5.6 months among patients with a best response of PD (n = 1), SD (n = 2), and VGPR (n = 1). All patients were alive at the end of the study.

Adverse Events

All 10 patients enrolled experienced at least 1 treatment-emergent AE (TEAE) (Table 2 and Supplemental Table 2 in the online version); however, no DLTs were reported in the safety run-in phase. Among patients in the safety run-in phase, the most common TEAE was neutropenia, followed by thrombocytopenia, anemia, fatigue, myalgia, nausea, and vomiting (3 [33.3%] patients each). Grade 3 or 4 TEAEs occurred in 6 (66.7%) patients in the safety run-in phase. The majority of the grade 3 or 4 TEAEs were hematologic AEs, including neutropenia, febrile neutropenia, thrombocytopenia, anemia, leukopenia, and lymphopenia. Three patients in the safety run-in phase had an SAE: 1 patient had grade 3 acute kidney injury (not considered related to treatment), 1 patient had grade 2 autoimmune encephalitis (an immune-mediated reaction possibly related to cetrelimab), and another patient had grade 3 febrile neutropenia and 2 septic shock events (one of grade 3 and another of grade 4 per investigator assessment; both grade 4 per Common Terminology Criteria for Adverse Events, V4.0; all SAEs in this patient were possibly related to daratumumab based on temporal association with study drug administration). The patient with grade 2 autoimmune encephalitis was hospitalized for cognitive deficits and behavioral changes ("déjà vu"). Laboratory tests showed polyclonal bands in the cerebrospinal fluid and ruled out infection. Electroencephalography with sleep deprivation failed to demonstrate epileptiform activity, but showed moderate left frontotemporal slowness. The patient received treatment with intravenous immunoglobulin and corticosteroids; after several days, the event was reported as resolved and the patient discharged. There were no deaths or discontinuation of study treatment owing to AEs.

IRRs occurred in 7 (77.8%) patients in the safety run-in phase. Most IRRs were grade 1 or 2, with no single event occurring in

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) Diagram



more than 2 patients (chills and cough in 2 [22.2%] patients each). One patient had a grade 3 IRR of dyspnea, and there were no grade 4 or 5 IRRs. None of the IRRs were deemed related to cetrelimab. No new malignancies were reported during the study, and no patients were positive for antibodies to daratumumab or cetrelimab.

Pharmacokinetics

Nine patients from the safety run-in phase were included in the PK-evaluable population for daratumumab and cetrelimab. The mean daratumumab C_{max} after the first dose (cycle 1 day 1 post-dose) was 304.99 μg/mL (SD, 60.0 μg/mL) (Figure 2A). Accumulation of daratumumab continued through the first 9 doses of weekly dosing (the last PK sampling time point in weekly dosing), resulting in a 3.3-fold increase in mean daratumumab concentration to a C_{max} of 1014.53 μg/mL (SD, 127.6 μg/mL) at cycle 3 day 1. The mean cycle 3 day 1 pre-dose C_{trough} after 8 weekly doses was 706.39 μg/mL (SD, 104.1 μg/mL). Moderate interpatient variability for daratumumab exposure (~30% coefficient of variation for post-dose) was observed.

The mean cetrelimab C_{max} after the first dose (cycle 1 day 2 post-dose) was 54.95 μg/mL (SD, 12.2 μg/mL) (Figure 2B). The mean observed C_{trough} for cetrelimab was 79.67 μg/mL (SD, 26.2 μg/mL) at cycle 3 day 1 (n = 6 patients). The mean C_{trough} at cycle 5 day 1 upon reaching steady state after 8 weekly doses was 101.31 μg/mL (SD, 4.2 μg/mL) (n = 2 patients). Moderate inter-patient variability for cetrelimab exposure (~30% coefficient of variation for post-dose) was observed.

Biomarkers

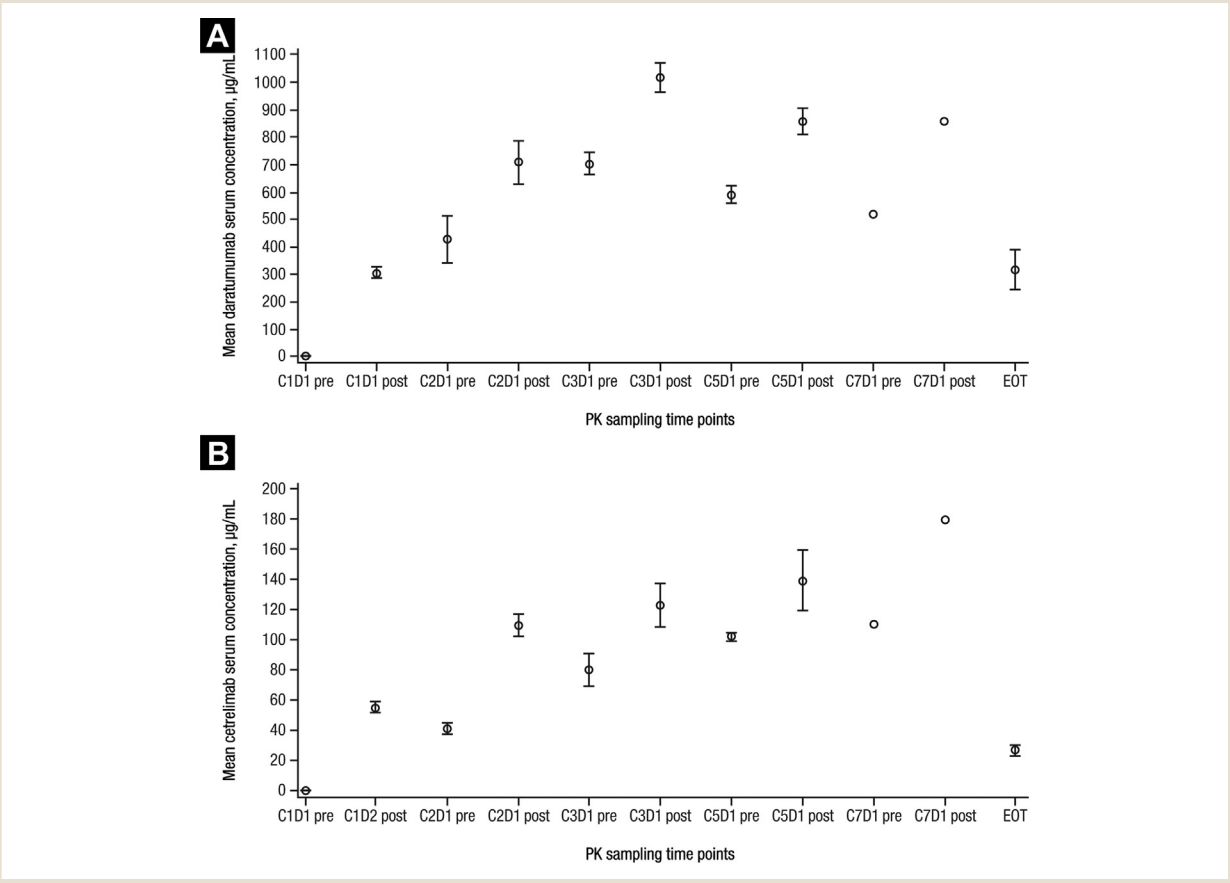
A decrease in NK cells post-treatment was observed (Figure 3A), providing further evidence that NK cells express CD38 and are sensitive to daratumumab-mediated depletion as a

Table 2 Treatment-emergent Adverse Events

Patients, n (%)	Safety Run-in (Daratumumab + Cetrelimab) (n = 9)
Any TEAEs	9 (100.0)
Related to daratumumab	9 (100.0)
Related to cetrelimab	8 (88.9)
Grade 3 or 4 TEAE	6 (66.7)
Grade 5 TEAE	0
Leading to discontinuation	0
Any serious TEAE	3 (33.3)
Related to daratumumab	1 (11.1)
Related to cetrelimab	1 (11.1)
TEAEs reported in ≥ 20% of patients	
Neutropenia	4 (44.4)
Thrombocytopenia	3 (33.3)
Anemia	3 (33.3)
Fatigue	3 (33.3)
Myalgia	3 (33.3)
Nausea	3 (33.3)
Vomiting	3 (33.3)
Asthenia	2 (22.2)
Chills	2 (22.2)
Cough	2 (22.2)
Diarrhea	2 (22.2)
Hypertension	2 (22.2)
Lymphopenia	2 (22.2)
Paresthesia	2 (22.2)
Infusion-related reactions	7 (77.7)

Abbreviation: TEAE = treatment-emergent adverse event.

Figure 2 Mean and Standard Deviation Serum Peak and Trough Concentrations of (A) Daratumumab and (B) Cetrelimab in the PK-Evaluable Analysis Set



Abbreviations: C = cycle; D = day; EOT = end of treatment; PK = pharmacokinetic; post = post-dose; pre = pre-dose.

pharmacodynamic biomarker. $CD38^+$ monocytic MDSCs and $CD38^+$ T_{regs} were also sensitive to daratumumab, showing depletion in the first 2 treatment cycles (Figure 3B and C, respectively). The number of $CD8^+$ T cells increased at approximately cycle 4 (Figure 3D).

Discussion

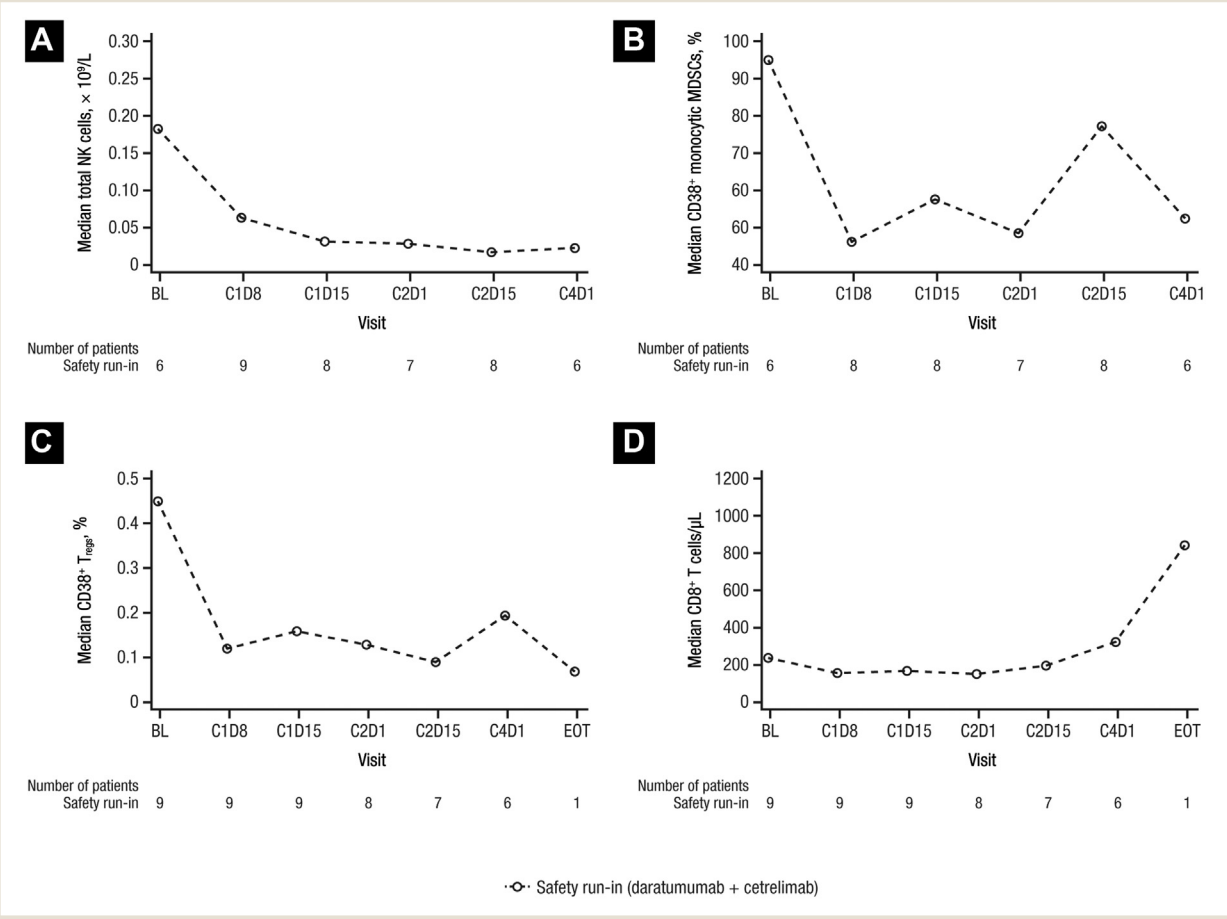
This multiple-phase study examined the safety and efficacy of daratumumab as combination therapy with cetrelimab in heavily pre-treated patients with RRMM, but the study was terminated by administrative closure. Owing to the relatively short median follow-up period (≤ 6.7 months) and the limited number of evaluable patients, most planned efficacy analyses were not performed. Nevertheless, the safety profiles of daratumumab and cetrelimab were generally consistent with their previously described safety profiles.[4,23-26]

Daratumumab leads to deep and durable responses as monotherapy or combination therapy with standard-of-care regimens for patients with RRMM, or as combination therapy for NDMM.[4,27-31] As monotherapy for RRMM among heavily pre-treated patients, daratumumab was associated with an ORR of 31.1%.[4] When combined with standard-of-care regimens for RRMM or NDMM, the ORRs were generally higher and ranged from 84% to 93%.[27-31] Although the ORR (44.4%) in the present study is generally consistent with response rates seen with daratumumab monotherapy, comparison to previous trials should be considered carefully owing to the limited follow-up time and small number of evaluable patients.

PK analyses of daratumumab in this study, including peak and trough serum concentrations, were comparable to those observed in prior studies of daratumumab,[32] and the combination of daratumumab with cetrelimab did not appear to alter the PK of daratumumab. Also consistent with previous data for daratumumab therapy,[32,33] no patients were positive for antibodies to daratumumab, and no patients were positive for antibodies to cetrelimab.

Although the biomarker analysis was limited by the number of evaluable samples, patients who received daratumumab plus cetrelimab showed a decrease in NK cells, $CD38^+$ MDSCs, and $CD38^+$ T_{regs} that is consistent with the known sensitivity of these cell populations to daratumumab.[10] Evaluation of total $CD8^+$ T-cell numbers at baseline and post-treatment with daratumumab in combination with cetrelimab showed an increase in absolute counts of $CD8^+$ T cells around cycle 4. This observation is also consistent

Figure 3 Immunophenotyping of Peripheral Blood Samples as Assessed by Flow Cytometry Among Patients in the Safety Run-in Phase. (A) Median Total NK Cells (Absolute Count) in Blood Over Time. (B) Median Percent of $CD38^+$ Monocytic MDSCs of Total MDSCs in Blood Over Time. (C) Median Percent of $CD38^+$ T_{regs} of Total T_{regs} in Blood Over Time. (D) Median Total $CD8^+$ T Cells (Absolute Count) in Blood Over Time



Abbreviations: BL = baseline; C = cycle; D = day; EOT = end of treatment; MDSC = myeloid-derived suppressor cell; NK = natural killer; T_{regs} = regulatory T cells.

with previous clinical data that showed daratumumab increases absolute counts of $CD8^+$ T cells.[10]

Checkpoint inhibitors have recently emerged as a highly promising type of immunotherapy for the treatment of a variety of malignancies. The pre-clinical finding of high PD-L1 expression in malignant plasma cells, coupled with evidence suggesting a role for PD-L1 in the development of myeloma clonal resistance and relapse, drove the field toward pursuing immune checkpoint inhibitors in myeloma.[13-15,34] Other studies have examined anti–PD-1 antibodies as monotherapy or as part of combination therapy in patients with MM. The phase Ib KEYNOTE-013 study evaluated the safety and efficacy of pembrolizumab, a humanized anti–PD-1 antibody, as monotherapy for patients with RRMM. In KEYNOTE-013, the ORR was 0% with 56.7% (17/30) of patients achieving SD after a median follow-up of 19.9 months.[35] Similarly, the anti–PD-1 antibody nivolumab showed limited therapeutic benefit as monotherapy or combination therapy with ipilimumab in patients with RRMM, with no patients achieving an objective response.[36,37]

In these studies of anti–PD-1 antibodies as monotherapies, no overt safety issues were reported, although these analyses were among a relatively small number of patients.[35,36] In the LUC2001 study of daratumumab plus the PD-L1 inhibitor atezolizumab in NSCLC, nearly all patients experienced a TEAE.[38] Serious TEAEs were more frequent in LUC2001 (occurring in 47.7% of patients) than in the current study of daratumumab with cetrelimab (33.3% of patients), but the clinical significance of this difference is unclear.

Early phase studies of pembrolizumab in combination with standard-of-care regimens for myeloma showed promising results,[17,18] but the therapeutic benefit of PD-1 inhibition for RRMM was called into question following results from the randomized phase III KEYNOTE-183 study.[39] In KEYNOTE-183, slightly more patients died in the pembrolizumab/pomalidomide/dexamethasone group versus the pomalidomide/dexamethasone alone group (23% vs. 17%, respectively, after a median follow-up of 7.8 vs. 8.6 months). Moreover, deaths in the pembrolizumab/pomalidomide/dexamethasone group were disproportionately owing to AEs compared with the control group (n = 13 vs. n = 3, respectively), and the study was

ended early owing to the unfavorable benefit-to-risk profile.[39] Similarly, the phase III KEYNOTE-185 study of pembrolizumab/lenalidomide/dexamethasone in transplant-ineligible patients with NDMM was terminated early owing to an imbalance in deaths in the pembrolizumab-combination group versus the control group.[40]

It is unclear whether the increased deaths observed in the KEYNOTE-183 and KEYNOTE-185 studies of pembrolizumab-combination therapy would also occur for the combination of daratumumab with an anti–PD-1 antibody, as daratumumab has a different mechanism of action than the IMiD drug partners tested with pembrolizumab in KEYNOTE-183 and KEYNOTE-185. The efficacy and safety of PD-L1 inhibitors have also come under scrutiny, with several studies being placed on partial holds or suspended. Enrollment was halted or suspended for the phase II FUSION MM-003 and FUSION MM-005 studies examining durvalumab with daratumumab in patients with RRMM, following advisement by the United States Food and Drug Administration based on the risks identified in other clinical trials evaluating PD-(L)1 inhibitors for the treatment of MM.[41]

Although the current study showed that combination therapy of daratumumab and cetrelimab did not cause DLTs, complete efficacy and PK analyses were limited for several reasons. Termination of the study owing to administrative closure resulted in a relatively small study population with a short treatment duration and follow-up. Additionally, as the planned Parts 2 and 3 of the study were not completed, there was no comparator arm. These limitations prevent meaningful interpretation of the efficacy and PK data.

Conclusion

Early closure of this study hindered the evaluation of efficacy, and prevented a complete analysis of safety, PK, and biomarkers. However, no new safety concerns were identified with the combination of daratumumab plus cetrelimab relative to the individual therapies, and no AEs led to treatment discontinuation or death. Further investigations into combination therapies including daratumumab plus PD-(L)1 inhibitors in MM may be warranted.

Clincial Practice Points

- Improved treatment options are needed for patients with RRMM.
- Data from pre-clinical and early-phase clinical studies of PD-(L)1 inhibitors suggest that cetrelimab plus daratumumab would have therapeutic potential for patients with RRMM.
- This study evaluated daratumumab with or without cetrelimab in patients with RRMM who failed on ≥ 3 prior lines of therapy (including a PI and an IMiD) or who were refractory to both.
- There were no DLTs in the safety run-in phase of the study, and no new safety concerns were identified.
- The study was terminated for administrative reasons shortly after the randomized phase began, limiting the complete evaluation on efficacy, safety, PK, and changes in biomarkers.

Acknowledgments

This study was sponsored by Janssen Research & Development, LLC. Editorial and medical writing support was provided by Charlotte D. Majerczyk, PhD, of MedErgy, and was funded by Janssen Global Services LLC. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. This work was supported by Janssen Research & Development, LLC.

Disclosure

YCC is an employee and has been compensated for a leadership position at VBL Therapeutics; consulted for Janssen, Takeda, Amgen, and Bristol-Myers Squibb; served on a speakers' bureau for and received research funding from Amgen; and received travel expenses from Amgen, Janssen, and Neopharm. AO consulted for and served on a speakers' bureau for Amgen, Celgene, Amgen, Takeda and Janssen. KLW consulted for Takeda, Janssen, and Amgen. NL has no disclosures to report. PV consulted for Celgene, Amgen, Takeda, and Janssen; and received travel expenses from Celgene and Takeda. JS-M consulted for and received honoraria from Amgen, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Karyopharm, Novartis, MSD, Takeda, Sanofi, and Roche. SL consulted for Celgene, Takeda, Amgen, Bristol-Myers Squibb, Janssen, GlaxoSmithKline, Karyopharm, and Genentech, and received research funding from Celgene, Takeda, and Janssen. CJ, WG, RC, WC, JF, HF, HX, and JS are employees of Janssen.

Supplemental Data

Supplemental Appendix, Tables and Figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.clml.2020.08.008.

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Supplemental Appendix

Additional Methods

Additional Eligibility Criteria

Key inclusion criteria were: age ≥ 18 years with documented, measurable relapsed or refractory multiple myeloma (MM) and had received at least 3 prior lines of therapy (including a proteasome inhibitor [PI] and an immunomodulatory agent [IMiD]) or were refractory to both a PI and an IMiD. Patients also had evidence of partial response or better to at least 1 prior treatment based on investigator's determination of response by the International Myeloma Working Group criteria,[19-21] an Eastern Cooperative Oncology Group performance status of 0 to 2; hemoglobin ≥ 7.5 g/dL; absolute neutrophil count ≥ 1.0×10^9/L; platelet count ≥ 75×10^9/L (≥ 50×10^9/L if ≥ 50% of the bone marrow is infiltrated with MM cells); aspartate aminotransferase and alanine aminotransferase each ≤ 2.5 × the upper limit of normal; total bilirubin ≤ 2.0 × upper limit of normal; estimated creatinine clearance ≥ 30 mL/min; and corrected serum calcium ≤ 14 mg/dL (or free ionized calcium ≤ 6.5 mg/dL).

Key exclusion criteria were: prior treatment with daratumumab or other anti-CD38 therapies or anti—programmed death receptor-1/programmed death-ligand 1 therapies; antimyeloma therapies within 2 weeks, except emergency use of a short course of corticosteroids (equivalent to dexamethasone 40 mg/day for ≤ 4 days) for palliative treatment prior to the first administration of study treatment; allogenic stem cell transplant (SCT) at any time or autologous SCT within 12 weeks of the first administration of study treatment; systemic radiotherapy within 14 days prior to the first dose of study treatment; clinical signs of meningeal involvement of MM; known chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 50% of predicted normal; known moderate or severe persistent asthma within the past 2 years or uncontrolled asthma; seropositivity for HIV, hepatitis B, or hepatitis C infection; clinically significant cardiac disease; history of malignancy other than MM within 2 years prior to the first dose of study therapy administration (except squamous and basal cell skin cancer and carcinoma in situ of the cervix); known allergies/hypersensitivity/intolerance to mannitol, corticosteroids, monoclonal antibodies, or human proteins or their excipients, or known sensitivity to mammalian-derived products; prior diagnosis of autoimmune disease; and vaccination with live attenuated vaccines within 4 weeks before the first dose of study therapy. Patients were also not permitted to have planned SCT prior to progression of disease on this study.

Pre- and Post-infusion Medications

Pre-infusion medications were administered to patients who received daratumumab to manage infusion-related reactions (IRRs). Pre-infusion medications were administered approximately 1 hour before the daratumumab infusion and included acetaminophen 650 to 1000 mg intravenously (IV) or orally (PO), diphenhydramine 25 to 50 mg IV or PO or equivalent antihistamine, and methylprednisolone 100 mg IV or PO or equivalent for the first 2 doses and 60 mg for subsequent doses (in the absence of IRRs in the first 2 doses). A leukotriene inhibitor (montelukast 10 mg PO) was optional and may have been administered up to 24 hours before the daratumumab infusion. Post-infusion medication included methylprednisolone 20 mg PO or equivalent on the 2 days after each daratumumab dose (oral corticosteroids could be given per investigator discretion after the first 3 doses). Patients with a higher risk of respiratory complications (eg, patients with mild asthma or patients with chronic obstructive pulmonary disease who have a forced expiratory volume in 1 second < 80%) could be given diphenhydramine or equivalent on the first and second day after each infusion, short-acting β2-adrenergic receptor agonist such as albuterol aerosol, and control medications for lung disease, as needed. If the at-risk patient experienced no major IRRs after 4 doses of study treatment, these post-infusion medications could be waived at the investigator's discretion.

Additional Results

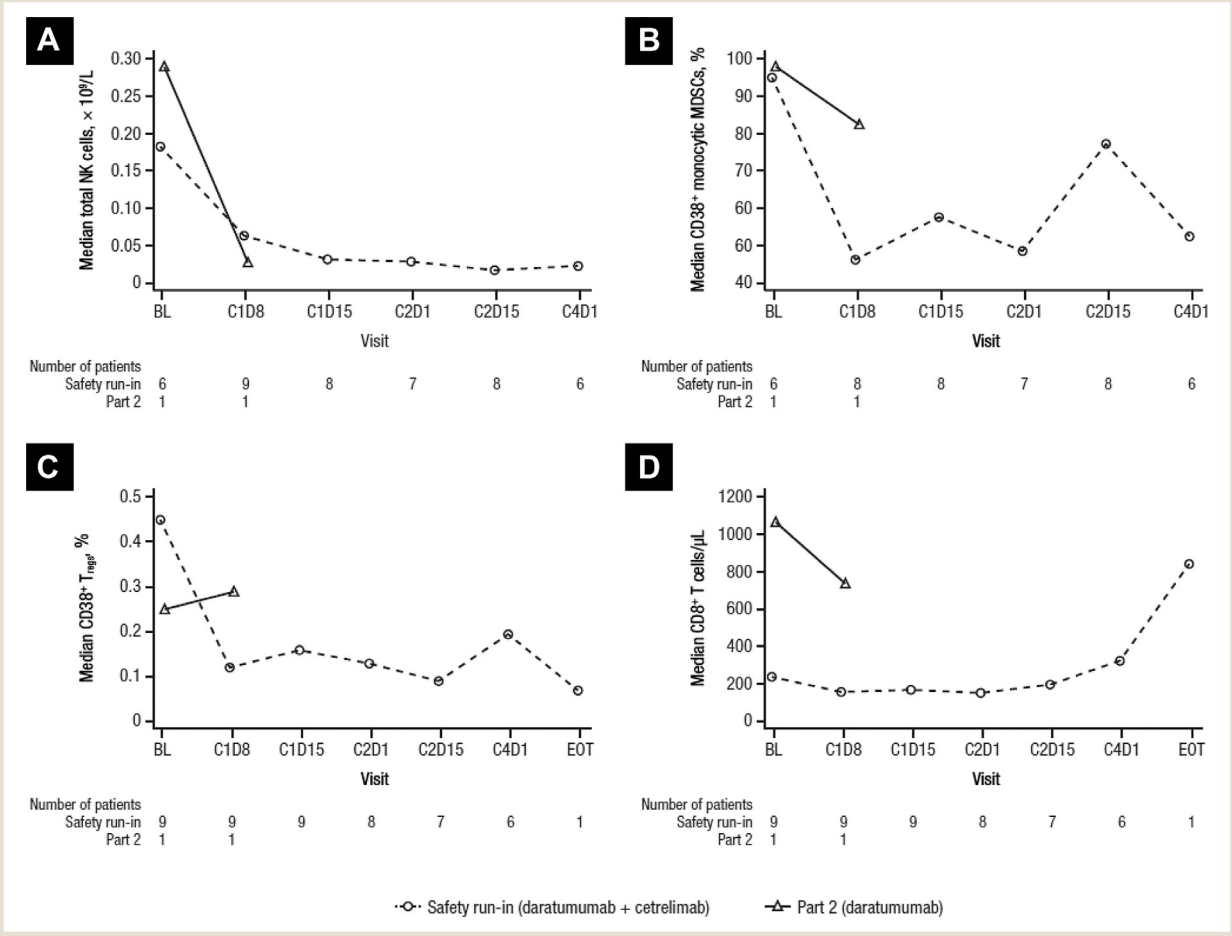
Single Randomized Patient in Part 2

The patient in Part 2 was a 43-year-old white male with a baseline Eastern Cooperative Oncology Group performance status score of 0, IgG disease isotype, standard cytogenetic risk, and a time from initial diagnosis to the first dose of study treatment of 52.2 months (see Supplemental Table 1 in the online version). The patient was previously treated with a PI inhibitor plus an IMiD, corticosteroids, alkylating agents, and had received autologous SCT.

The patient who enrolled in Part 2 withdrew consent 7 days after receiving the first daratumumab dose, with a follow-up time of 0.3 months. This patient received 2 of 4 planned daratumumab infusions at 100.9% relative dose intensity in the first cycle over 0.3 months.

The patient enrolled in Part 2 was not evaluable for disease response.

Supplemental Figure 1 **Immunophenotyping of Peripheral Blood Samples as Assessed by Flow Cytometry in the Safety Analysis Set (all Patients). (A) Median Total NK Cells (Absolute Count) in Blood Over Time. (B) Median Percent of CD38$^+$ Monocytic MDSCs of Total MDSCs in Blood Over Time. (C) Median Percent of CD38$^+$ T_{regs} of Total T_{regs} in Blood Over Time. (D) Median Total CD8$^+$ T Cells (Absolute Count) in Blood Over Time**



Abbreviations: BL = baseline; C = cycle; D = day; EOT = end of treatment; MDSC = myeloid-derived suppressor cell; NK = natural killer; T_{regs} = regulatory T cells.

Supplemental Table 1 Patient Demographic and Disease Characteristics

Characteristic	Safety Run-in (Daratumumab + Cetrelimab) (n = 9)	Part 2 (daratumumab) (n = 1)	All Patients (N = 10)
Median (range) age, y	64.0 (44-79)	43.0	64.0 (43-79)
Male, n (%)	5 (55.6)	1 (100.0)	6 (60.0)
Race, n (%)			
White	8 (88.9)	1 (100.0)	9 (90.0)
Black or African American	1 (11.1)	0	1 (10.0)
Ethnicity, n (%)			
Not Hispanic/Latino	9 (100.0)	1 (100.0)	10 (100.0)
ECOG performance status, n (%)			
0	6 (66.7)	1 (100.0)	7 (70.0)
1	3 (33.0)	0	3 (30.0)
Type of myeloma, n (%)[a]			
IgG	3 (33.3)	1 (100.0)	4 (40.0)
IgA	2 (22.2)	0	2 (20.0)
IgM	1 (11.1)	0	1 (10.0)
Light chain (Kappa)	1 (11.1)	0	1 (10.0)
Negative immunofixation	2 (22.2)	0	2 (20.0)
ISS disease stage, n (%)			
I	5 (55.6)	0	5 (50.0)
II	3 (33.3)	0	3 (30.0)
III	1 (11.1)	1 (100.0)	2 (20.0)
Cytogenetic profile, n (%)			
Standard risk	9 (100.0)	1 (100.0)	10 (100.0)
Number of lines of prior therapy			
Median (range)	3.0 (2-5)	3	3.0 (2-5)
Patients with $\leq$ 3 prior lines, n (%)	5 (55.6)	1 (100.0)	6 (60.0)
Patients with $>$ 3 prior lines, n (%)	4 (44.4)	0	4 (40.0)
Median (range) time from diagnosis to first dose, mo	50.6 (16.4-287.0)	52.2	51.4 (16.4-287.0)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; Ig = immunoglobulin; ISS = International Staging System.
[a]By immunofixation or serum free light chain assay.

Supplemental Table 2 Treatment-emergent Adverse Events

Patients, n (%)	Safety Run-in (Daratumumab + Cetrelimab) (n = 9)	Part 2 (Daratumumab) (n = 1)	All Patients (N = 10)
Any TEAEs	9 (100.0)	1 (100.0)	10 (100.0)
Related to daratumumab	9 (100.0)	0	9 (90.0)
Related to cetrelimab	8 (88.9)	–	8 (80.0)
Grade 3 or 4 TEAE	6 (66.7)	1 (100.0)	7 (70.0)
Grade 5 TEAE	0	0	0
Leading to discontinuation	0	0	0
Any serious TEAE	3 (33.3)	0	3 (30.0)
Related to daratumumab	1 (11.1)	0	1 (10.0)
Related to cetrelimab	1 (11.1)	0	1 (10.0)
TEAEs reported in ≥ 20% of patients			
Neutropenia	4 (44.4)	0	4 (40.0)
Thrombocytopenia	3 (33.3)	1 (100.0)	4 (40.0)
Anemia	3 (33.3)	0	3 (30.0)
Fatigue	3 (33.3)	0	3 (30.0)
Myalgia	3 (33.3)	0	3 (30.0)
Nausea	3 (33.3)	0	3 (30.0)
Vomiting	3 (33.3)	0	3 (30.0)
Asthenia	2 (22.2)	0	2 (20.0)
Chills	2 (22.2)	0	2 (20.0)
Cough	2 (22.2)	0	2 (20.0)
Diarrhea	2 (22.2)	0	2 (20.0)
Hypertension	2 (22.2)	0	2 (20.0)
Lymphopenia	2 (22.2)	0	2 (20.0)
Paresthesia	2 (22.2)	0	2 (20.0)
Infusion-related reactions	7 (77.7)	0	7 (70.0)

Abbreviation: TEAE = treatment-emergent adverse event.