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A Phase I First-in-Human Study of ABBV-383, a B-Cell Maturation Antigen × CD3 Bispecific T-Cell Redirecting Antibody, in Patients With Relapsed/Refractory Multiple Myeloma

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PURPOSE ABBV-383, a B-cell maturation antigen × CD3 T-cell engaging bispecific antibody, has demonstrated promising results in an ongoing first-in-human phase I study (ClinicalTrials.gov identifier: [NCT03933735](https://clinicaltrials.gov/ct2/show/study/NCT03933735)) in patients with relapsed/refractory multiple myeloma (RRMM). Herein, we report safety and efficacy outcomes of this phase I dose escalation/expansion study.

METHODS Patients with RRMM (≥ three prior lines including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody) were eligible. ABBV-383 was administered intravenously over 1-2 hours once every 3 weeks, without any step dosing. A 3 + 3 design with backfilling for dose escalation was used (inpatient escalation to highest safe dose permitted) followed by initiation of dose expansion.

RESULTS As of January 8, 2022, 124 patients (dose escalation [0.025-120 mg], n = 73; dose expansion [60 mg], n = 51) have received ABBV-383; median age was 68 years (range, 35-92 years). The most common hematologic treatment-emergent adverse events (TEAEs) were neutropenia (all grades: 37%) and anemia (29%). The most common nonhematologic TEAEs were cytokine release syndrome (57%) and fatigue (30%). Seven deaths from TEAEs were reported with all considered unrelated to study drug by the investigator. For all efficacy-evaluable patients (n = 122; all doses), the objective response rate (ORR) was 57% and very good partial response (VGPR) or better (≥ VGPR) rate was 43%. In the 60 mg dose expansion cohort (n = 49), the ORR and ≥ VGPR rates were 59% and 39%, respectively; and in the ≥ 40 mg dose escalation plus dose expansion cohorts (n = 79) were 68% and 54%, respectively.

CONCLUSION ABBV-383 in patients with RRMM was well tolerated with an ORR of 68% at doses ≥ 40 mg. This novel therapy's promising preliminary antitumor activity in heavily pretreated patients warrants further clinical evaluation.

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INTRODUCTION

Multiple myeloma (MM) is the second most prevalent hematologic malignancy globally.¹ Treatment options for MM have improved substantially over the past 20 years, with many new drug classes, such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies (mAbs), being introduced that have increased life expectancy.² Despite these advances, patients will ultimately develop drug-resistant disease and progress to relapsed/refractory multiple myeloma (RRMM). Thus, patients with RRMM represent a significant treatment challenge, as they have a poor prognosis.³

Survival is limited in patients with RRMM with a median overall survival (OS) of 5.6-11.2 months in patients

refractory to CD38-targeted mAbs⁴ and a median OS of 5.1-11.5 months in patients who are double or triple/quadruple refractory to PIs and IMiDs.^{3,5} Drug resistance, which represents an important challenge for the treatment of RRMM, is due to a number of possible mechanisms including changes in the tumor microenvironment, clonal evolution, P-glycoprotein overexpression in MM cells, and multidrug resistance gene polymorphism.⁶ Therefore, there is still a need to develop new therapies with novel mechanisms of action to target RRMM cells effectively and improve treatment outcomes and overall quality of life for patients.

B-cell maturation antigen (BCMA), also known as tumor necrosis factor receptor superfamily member 17 or CD269, is a type III transmembrane glycoprotein

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

There remains an unmet clinical need for novel therapies that can overcome treatment resistance and improve overall outcomes for patients with relapsed/refractory multiple myeloma. B-cell maturation antigen has emerged as a promising therapeutic target in multiple myeloma. This trial describes outcomes with ABBV-383, an anti B-cell maturation antigen × CD3 bispecific monoclonal antibody in patients with relapsed/refractory multiple myeloma (\geq three prior lines of therapy: proteasome inhibitor, immunomodulatory drug, and anti-CD38 monoclonal antibody).

Knowledge Generated

ABBV-383 was well tolerated in the overall population (N = 124), with cytokine release syndrome (57%) the most common treatment-emergent adverse event; majority of events were grades 1/2 (55%). An objective response rate of 68% and \geq very good partial response rate of 54% were reported at the therapeutic doses of \geq 40 mg. Median duration of response and progression-free survival were not reached (median follow-up: 10.8 months).

Relevance

The promising preliminary antitumor activity in heavily pretreated patients supports further exploration of ABBV-383 in patients with multiple myeloma in larger clinical trials.

that is highly expressed on MM cells, but not on other normal tissues aside from normal plasma cells.^{7,8} BCMA is involved in the regulation of B-cell proliferation, survival, maturation, and differentiation into plasma cells.⁷ Thus, BCMA has emerged as a novel treatment target for MM because of its highly selective expression on malignant plasma cells.^{8,9} A number of BCMA-targeted therapies are being developed, including chimeric antigen receptor–modified T-cell (CAR-T) therapies, antibody-drug conjugates (ADCs), and T-cell engaging bispecific mAbs (T-BsAbs),⁷⁻⁹ and some have received approval (accelerated and/or full approval) by the US Food and Drug Administration and the European Medicines Agency. Approved agents include belantamab mafodotin (first-in-class anti-BCMA immunoglobulin [Ig]G1 ADC), idecabtagene vicleucel, and ciltacabtagene autoleucel (BCMA-targeted CAR-T therapies).¹⁰⁻¹⁵

ABBV-383 (formerly known as TNB-383B), is a next-generation, fully human, monoclonal, IgG4 T-BsAb, BCMA-targeted therapy, which incorporates a low-activating CD3 that preclinically decouples T-cell activation from cytokine release and preferentially activates effector over regulatory T cells.¹⁶⁻¹⁸ ABBV-383 consists of two heavy chains and one light chain: heavy chain 1 and the kappa light chain form the antigen-binding site that recognizes and binds to human CD3 with low affinity (1.3 μ M), whereas heavy chain 2 targets BCMA with high affinity and avidity.^{16,18} The unique design of ABBV-383 maximizes MM target-cell killing while potentially minimizing off-target toxicity and cytokine release, as demonstrated in preclinical studies. These results may translate to the improved tolerability and efficacy in vivo.¹⁸ ABBV-383 has demonstrated antitumor cell activity with minimal cytokine release in preclinical studies.^{16,17} Ex vivo efficacy was also demonstrated against bone marrow mononuclear cells freshly isolated from patients with relapsed MM, with only a mild

increase of cytokines associated with cytokine release syndrome (CRS).¹⁸

Herein, we report interim results from the first-in-human phase I trial that is currently ongoing to investigate the safety, clinical pharmacology, and clinical activity of ABBV-383 in patients with RRMM.

METHODS

Study Design

To our knowledge, this study was the first-in-human, phase I, multicenter, open-label clinical trial of ABBV-383 that consisted of a dose escalation phase followed by dose-expansion phase. The primary objectives of the study evaluated the safety and tolerability, determined the maximum tolerated dose (MTD) or recommended phase II dose, and evaluated clinical pharmacology of ABBV-383 monotherapy. The secondary objective evaluated the clinical activity of ABBV-383 monotherapy according to the 2016 International Myeloma Working Group (IMWG) criteria.¹⁹

All patients provided written informed consent before study entry. The study was approved by the relevant institutional review boards and/or independent ethics committees, and was conducted according to the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. This study is registered with ClinicalTrials.gov (identifier: [NCT03933735](https://clinicaltrials.gov/ct2/show/study/NCT03933735)).

Patient Eligibility

Full eligibility criteria are listed in the Appendix [Table A1](#) (online only). Briefly, patients (age \geq 18 years) with RRMM (\geq three prior lines of therapy that included a PI, an IMiD, and an anti-CD38 mAb), estimated glomerular filtration rate \geq 30 mL/min as calculated by the Modification of Diet in Renal Disease formula, and Eastern Cooperative Oncology Group performance status (ECOG PS) score \leq 2 were

enrolled. Prior treatment with a BCMA-targeted therapy was prohibited, and patients were not candidates for treatment regimens known to provide clinical benefit in MM.

Dose Escalation and Dose Expansion Phases

Patients received ABBV-383 intravenously (IV) over 1-2 hours at a fixed dose once every 3 weeks in the dose escalation phase (Appendix Fig A1, online only). No step or priming doses were implemented. Patients were premedicated with dexamethasone 10 mg IV (once on day 1) or equivalent prior to the administration of ABBV-383 for cycle 1. Subsequently, the dose frequency would be prior to the administration of ABBV-383 only (once every 3 weeks) and it could be tapered off as stated in the Protocol (online only) for subsequent cycles. If a patient did not experience an infusion-related reaction or immune-mediated toxicity in a given cycle, the dexamethasone premedication dose could be reduced to 5 mg IV (once on day 1) thereafter prior to the administration of ABBV-383 (once every 3 weeks). If a patient did not experience an infusion-related reaction or immune-mediated toxicity in a cycle where they received 5 mg dexamethasone IV (once on day 1) as premedication, dexamethasone could subsequently be omitted from the premedication regimen prior to the administration of ABBV-383 (once every 3 weeks). Additional administration details are provided in the Appendix 1 (online only). Fourteen dose levels were evaluated: 0.025 mg, 0.075 mg, 0.2 mg, 0.6 mg, 1.8 mg, 5.4 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 90 mg, and 120 mg. Patients received ABBV-383 until progressive disease (PD), unacceptable toxicity, or up to 3 years after the last patient's first dose.

The study used a 3 + 3 design with backfilling for selected doses and permitted inpatient escalation to highest safe dose. In the dose escalation phase, cohorts 1-3 planned to enroll single patients, and beginning at cohort 4, a standard 3 + 3 dose escalation design was planned. Single-patient cohorts were planned to be converted to 3 + 3 cohorts if grade ≥ 2 toxicity was observed or if deemed appropriate by the safety monitoring group (eg, medical monitors and principal investigators or designated subinvestigators). Upon completion of the first cycle of the prior dose level, patients were able to inpatient dose escalate to the next dose level following a review of the safety data from the higher dose by the safety monitoring group. Escalation-dose decisions were based on clinically significant toxicity, dose-limiting toxicity (DLT) events, and pharmacokinetic (PK) and pharmacodynamic findings. DLTs were determined during the first 21-day cycle and defined as a treatment-emergent adverse event (TEAE) not reasonably attributed to the patient's underlying disease, other medical conditions, or concomitant medications or procedures. The MTD was defined as the highest dose level at which < 2 of six evaluable patients experience a DLT.

At the time of the data cutoff, enrollment of the 60 mg expansion cohort had been completed, and the protocol was in process of being amended to investigate a lower

dose (40 mg once every 3 weeks) in an additional expansion cohort (Appendix Fig A1). Patients were allowed to receive ABBV-383 as long as they did not meet discontinuation criteria or complete the study.

Assessments

Safety was assessed during the study through the evaluation of TEAEs, laboratory profiles, physical examinations, and vital signs. TEAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. TEAEs were captured from the time of consent until 90 days after discontinuation of ABBV-383. Serious TEAEs met the following criteria: death of patient, life-threatening, involved hospitalization, significant disability/incapacity, or required medical/surgical intervention to prevent serious outcome.

Blood samples for ABBV-383 PK analysis and antidrug antibody (ADA) analysis were collected at designated time points throughout the study and analyzed using the validated assays. PK parameters of ABBV-383 were determined using noncompartmental methods. Immunogenicity of ABBV-383 was summarized on the basis of the available ADA data.

Efficacy was assessed using 2016 IMWG uniform response criteria,¹⁹ including the objective response rate (ORR; defined as confirmed stringent complete response [sCR] plus complete response [CR] plus very good partial response [VGPR] plus partial response [PR]), OS, progression-free survival (PFS), time-to-progression, time-to-response, and duration of response (DoR). IMWG laboratory assessments (serum protein electrophoresis, urine protein electrophoresis, serum and urine immunofixation, serum free light chains, and serum quantitative immunoglobulins) were performed by a central laboratory. Imaging assessments were performed locally. All response categories required two consecutive assessments for confirmation. Minimal residual disease (MRD) was assessed by immunoglobulin gene rearrangement sequencing (Adaptive Biotechnologies, Seattle, WA) on bone marrow aspirate DNA at the time of suspected CR/sCR. PFS was defined as the time from the first dose of ABBV-383 to PD or death, whichever occurred first. OS was defined as the time from the first dose of ABBV-383 to death due to any cause. Patients were censored at the last known alive date on or before the data cutoff or snapshot date if no death occurred. Time-to-progression was defined as the duration from start of treatment to PD. Time-to-response was defined as the time of start of study treatment to first confirmed response (\geq PR). The DoR was defined as the time from the initial objective response to PD or death, whichever occurred first; patients were censored at the date of last tumor assessment if neither event occurred.

Statistical Analysis

The safety population included all patients who received ≥ 1 dose of ABBV-383. The efficacy-evaluable population was defined as patients who received ≥ 1 dose of ABBV-383 and have ≥ 1 postdose disease assessment. The PK

TABLE 1. Patient Characteristics

Characteristic	60 mg EXP (n = 51)	≥ 40 mg ESC + EXP (n = 81)	All Patients (N = 124)
Median age, years (range)	68 (35-92)	68 (35-92)	68 (35-92)
Male, No. (%)	26 (51)	44 (54)	68 (55)
Race, No. (%)			
White	40 (78)	63 (78)	98 (79)
Black or African American	7 (14)	13 (16)	20 (16)
Asian	1 (2)	1 (1)	1 (1)
Not reported	3 (6)	4 (5)	5 (4)
Ethnicity, No. (%)			
Hispanic	2 (4)	3 (4)	5 (4)
Not Hispanic or Latino	49 (96)	78 (96)	119 (96)
ECOG PS score, ^a No. (%)			
0	20 (39)	31 (38)	40 (32)
1	27 (53)	44 (54)	71 (57)
2	3 (6)	4 (5)	11 (9)
Median time since initial diagnosis to screening, years (range)	6 (1-15)	6 (1-17)	7 (0-20)
Revised ISS stage at entry, ^b No. (%)			
I	9 (18)	14 (17)	19 (15)
II	12 (24)	17 (21)	23 (19)
III	15 (29)	24 (30)	38 (31)
High-risk cytogenetics, ^c No. (%)	6 (12)	11 (14)	22 (18)
Median prior lines of therapy, No. (range)	4 (3-12)	4 (3-12)	5 (3-15)
Prior MM therapy, No. (%)			
Autologous SCT	42 (82)	67 (83)	100 (81)
Anti-CD38 antibody refractory	49 (96)	78 (96)	120 (97)
Double refractory ^d	45 (88)	68 (84)	104 (84)
Triple-class exposed	50 (98)	80 (99)	123 (99)
Triple-class refractory ^e	43 (84)	66 (81)	102 (82)
Penta-class exposed	45 (88)	74 (91)	113 (91)
Penta-class refractory ^f	23 (45)	33 (41)	44 (35)
Refractory to last prior cancer therapy, ^g No. (%)	43 (84)	69 (85)	108 (87)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ESC, dose escalation; EXP, dose expansion; IMiD, immunomodulatory drug; ISS, International Staging System; MM, multiple myeloma; PI, proteasome inhibitor; SCT, stem-cell transplant.

^aData missing in two patients.

^bUnknown: all patients, n = 44 (35%); ≥ 40 mg ESC + EXP, n = 26 (32%); 60 mg EXP, n = 15 (29%).

^cHigh-risk cytogenetics was defined as the presence of t(4;14), t(14;16), or 17p deletion as detected by fluorescence in situ hybridization analysis of CD138-enriched bone marrow aspirates performed at screening.

^dRefractory to a PI and an IMiD.

^eRefractory to an IMiD, a PI, and anti-CD38 antibody.

^fRefractory to ≥ 2 PIs, ≥ 2 IMiDs, and ≥ 1 anti-CD38 antibody.

^gProgressive disease on or within 60 days of last treatment regimen.

population included patients who received ≥ 1 dose of ABBV-383 and had ≥ 1 PK sample drawn.

Frequency distributions were used for categorical variables and appropriate summary statistics (mean, median, and range) for quantitative/continuous variables. The two-sided 80% exact binomial CIs of the ORR are summarized using the Clopper-Pearson method together with the best overall

response (CR, PR, stable disease, and PD). The Kaplan-Meier method was used to estimate PFS, OS, and DoR. Descriptive statistics for continuous safety variables and frequencies/percentages for discrete safety variables were used. The safety population allowed for detection of serious TEAEs occurring in as few as 21% of patients with 80% confidence.

TABLE 2. Patient Disposition

Disposition	60 mg EXP (n = 51)	≥ 40 mg ESC + EXP (n = 81)	All Patients (N = 124)
Treatment ongoing, No. (%)	23 (45)	38 (47)	45 (36)
Discontinued treatment, No. (%)	28 (55)	43 (53)	79 (64)
PD	21 (41)	31 (38)	60 (48)
DLT/AE	2 (4)	4 (5)	7 (6)
Physician decision	2 (4)	2 (2)	4 (3)
Cancer-related surgery/anticancer therapy	0	1 (1)	1 (1)
Withdrawal of consent	3 (6)	4 (5)	5 (4)
Discontinued study, No. (%)	15 (29)	25 (31)	55 (44)
Death	9 (18)	14 (17)	33 (27)
Withdrawal of consent	3 (6)	8 (10)	15 (12)
Lost to follow-up, No. (%)	0	0	1 (1)
Deaths, No. (%)	9 (18)	14 (17)	33 (27)
> 30 days from last dose	7 (14)	12 (15)	30 (24)
≤ 30 days from last dose	2 (4)	2 (2)	3 (2)
> 90 days from last dose	3 (6)	5 (6)	12 (10)
≤ 90 days from last dose	6 (12)	9 (11)	21 (17)
Median follow-up, months (range)	8.2 (0.6-11.5)	9.6 (0.6-18.2)	10.8 (0.6-28.2)

Abbreviations: AE, adverse event; DLT, dose-limiting toxicity; ESC, dose escalation; EXP, dose expansion; PD, progressive disease.

RESULTS

Patient Demographics and Baseline Characteristics

As of January 8, 2022, 124 patients were enrolled (escalation phase, n = 73; expansion phase, n = 51). Demographics and baseline characteristics of treated patients (N = 124) are shown in Table 1 and includes patients treated in the ≥ 40 mg escalation- plus expansion-phase cohorts (n = 81) and 60 mg expansion cohort (n = 51). In the overall population, the median age was 68 years (range, 35-92 years), 55% were male, and 57% had an ECOG PS score of 1. The median number of prior lines of therapy was 5 (range, 3-15 lines), and 87% of patients were refractory to the last prior therapy. Patient disposition is shown in Table 2. Treatment is ongoing in 45 (36%) patients, and 79 (64%) patients discontinued treatment, mostly because of PD (n = 60/79; 76%). Fifty-five (44%) patients discontinued study participation; reasons included death (n = 33; 27%), withdrawal of consent (n = 15; 12%), and lost to follow-up (n = 1; 1%). Of the 33 (27%) reported deaths, 30 occurred > 30 days from the last dose of ABBV-383 and three occurred ≤ 30 days from the last dose; 12 occurred > 90 days from last ABBV-383 dose and 21 occurred ≤ 90 days from last dose.

Safety

TEAEs (all grades, grade ≥ 3) in the overall population (N = 124), ≥ 40 mg escalation plus expansion (n = 81), and 60 mg expansion cohorts (n = 51) are shown in Table 3. The proportion of patients experiencing a TEAE (all grades) was similar in the overall population (98%), ≥ 40 mg

escalation plus expansion (99%), and 60 mg expansion cohorts (98%); 72%, 77%, and 78%, respectively, experienced a grade ≥ 3 TEAE. The most common hematologic TEAEs (all grades [≥ 25% total patients]/grade ≥ 3) in the overall population were neutropenia (37%/34%) and anemia (29%/16%); similar results were reported for the ≥ 40 mg escalation plus expansion and 60 mg expansion cohorts. The most common nonhematologic TEAEs (all grades [≥ 25% total patients]) in the overall population were CRS (57%), fatigue (30%), nausea (29%), and diarrhea (27%); and in the ≥ 40 mg escalation plus expansion/60 mg expansion (all grades [≥ 30% of patients]) were CRS (73%/71%), nausea (35%/31%), diarrhea (32%/29%), and fatigue (30%/29%). Hypogammaglobulinemia occurred in 17 (14%) patients in the overall population. Twenty-nine (23%) patients in the overall population required administration of immunoglobulins (intravenous, n = 15 [12%]; not otherwise specified, n = 14 [11%]; preferred terms have the potential for overlapping).

In the overall population, serious TEAEs occurred in 66 (53%) patients, of whom 48 (59%) patients received ≥ 40 mg doses of ABBV-383 (escalation plus expansion cohorts, n = 81) and 31 (61%) patients received 60 mg (expansion cohort, n = 51). TEAEs of infection occurred in 51 (41%) patients overall (≥ 40 mg escalation plus expansion cohorts: n = 36/51, 44%; 60 mg expansion cohort: n = 24/51, 47%); 31 (25%) patients reported serious events. Grade ≥ 3 events of infections (≥ 5% total patients) in the overall population were pneumonia, sepsis, COVID-19 disease (6% each), and urinary tract infections (5%).

TABLE 3. TEAEs

TEAE	60 mg EXP (n = 51)	≥ 40 mg ESC + EXP (n = 81)	All Patients (N = 124 ^a)
Leading to study drug discontinuation, No. (%)	3 (6)	6 (7)	12 (10)
Leading to study drug interruption, No. (%)	20 (39)	36 (44)	46 (37)
Leading to dose reduction, No. (%)	4 (8)	6 (7)	6 (5)
Associated with DLT, No. (%)	0	3 (4)	3 (2)
Leading to death, No. (%)	1 (2)	4 (5)	7 (6)

TEAEs (any grade) Occurring in ≥ 15% of Total Patients	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any, No. (%)	50 (98)	40 (78)	80 (99)	62 (77)	121 (98)	89 (72)
Hematologic, No. (%)						
Neutropenia ^b	21 (41)	18 (35)	37 (46)	33 (41)	46 (37)	42 (34)
Anemia	17 (33)	7 (14)	28 (35)	14 (17)	36 (29)	20 (16)
Thrombocytopenia ^c	13 (25)	5 (10)	20 (25)	9 (11)	29 (23)	15 (12)
Lymphopenia ^d	11 (22)	10 (20)	16 (20)	13 (16)	19 (15)	16 (13)
Nonhematologic, No. (%)						
CRS	36 (71)	1 (2)	59 (73)	3 (4)	71 (57)	3 (2)
Fatigue	15 (29)	0	24 (30)	0	37 (30)	1 (1)
Nausea	16 (31)	0	28 (35)	2 (2)	36 (29)	2 (2)
Diarrhea	15 (29)	1 (2)	26 (32)	1 (1)	34 (27)	2 (2)
Vomiting	10 (20)	0	23 (28)	0	30 (24)	0
Pyrexia	11 (22)	0	17 (21)	0	24 (19)	0
Arthralgia	6 (12)	0	12 (15)	0	22 (18)	0
Cough	11 (22)	0	16 (20)	0	20 (16)	0
Headache	4 (8)	0	10 (12)	1 (1)	20 (16)	2 (2)
Pain in extremity	8 (16)	0	14 (17)	0	20 (16)	0

Abbreviations: AE, adverse event; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; ESC, dose escalation; EXP, dose expansion; TEAE, treatment-emergent adverse event.

^aSafety population defined as patients who have received ≥ 1 dose of ABBV-383.

^bNeutropenia includes neutropenia, neutrophil count decreased, and febrile neutropenia.

^cThrombocytopenia includes platelet count decrease.

^dLymphopenia includes lymphocyte count decrease.

TABLE 4. CRS: Rate and Grade

CRS	60 mg EXP (n = 51)	≥ 40 mg ESC + EXP (n = 81)	All Patients (N = 124)
All grades, No. (%)	36 (71)	59 (73)	71 (57)
Grade 1, No. (%)	25 (49)	38 (47)	44 (35)
Grade 2, No. (%)	10 (20)	18 (22)	24 (19)
Grade ≥ 3, No. (%)	1 (2)	3 (4)	3 (2)
Serious, No. (%)	15 (29)	21 (26)	22 (18)
Median time to onset, days (range)	1 (1-2)	1 (1-2)	1 (1-7)
Median time to resolution, days (range)	1 (1-8)	1 (1-8)	1 (1-8)
Recurrent CRS after cycle 1, No. (%)	0	1 (1)	1 (1)

NOTE. Severity of the CRS is uniformly graded according to NCI CTCAE v5.0. Grade ≥ 3 events include one patient from the dose escalation cohort 14 (120mg once every 3 weeks) with initially reported severity of CRS as grade 3 because of transient organ toxicity in addition to pyrexia with absence of hypotension or hypoxia. This CRS event was subsequently adjudicated by the investigator to grade 1 severity to align with the CRS grading by NCI CTCAE v5.0.

Abbreviations: CRS, cytokine release syndrome; ESC, dose escalation; EXP, dose expansion; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

TABLE 5. Response Rates by IMWG Criteria

Overview of Efficacy	≥ 40 mg ESC + EXP (n = 79)	Triple-Class Refractory ^a (≥ 40 mg ESC + EXP) (n = 64)	60 mg EXP (n = 49)	Triple-Class Refractory ^a (60 mg EXP) (n = 41)	Total (N = 122)
ORR, No. (%)	54 (68)	40 (63)	29 (59) ^b	22 (54)	69 (57)
≥ VGPR, No. (%)	43 (54)	33 (52)	19 (39)	15 (37)	52 (43)
Best overall response, No. (%)					
sCR	16 (20)	12 (19)	4 (8)	3 (7)	21 (17)
CR	13 (16)	12 (19)	7 (14)	7 (17)	14 (11)
VGPR	14 (18)	9 (14)	8 (16)	5 (12)	17 (14)
PR	11 (14)	7 (11)	10 (20)	7 (17)	17 (14)
MR	1 (1)	1 (2)	1 (2)	1 (2)	2 (2)
SD ^c	18 (23)	17 (27)	14 (29)	13 (32)	36 (30)
PD	6 (8)	6 (9)	5 (10)	5 (12)	15 (12)

Abbreviations: CR, complete response; ESC, dose escalation; EXP, dose expansion; IMWG, International Myeloma Working Group; MR, minor response; ORR, objective response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response; ≥ VGPR, VGPR or better.

^aRefractory to an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody; programmatically derived confirmed or unconfirmed response (IMWG 2016).

^bTotal values because of rounding.

^cInclusive of unconfirmed VGPR (2 out of 36 patients) and unconfirmed PD (8 out of 36 patients).

In the overall population, TEAEs leading to discontinuation, interruption, or dose reduction of ABBV-383 occurred in 12 (10%), 46 (37%), and six (5%) patients, respectively; neutrophil count decrease was the most common TEAE (n = 15; 12%) leading to interruption of ABBV-383, and CRS was the most common TEAE (n = 3; 2%) leading to dose reduction. Three patients experienced DLTs (DLT population: N = 73), all within the escalation cohorts (platelet count decreased [grade 4; 60 mg] and CRS [grade 3; 90 mg and 120 mg]). The MTD for ABBV-383 was not reached during the dose escalation phase, and dose-expansion was initiated with the 60 mg dose of ABBV-383 once every 3 weeks on the basis of CRS, plateauing ORR, and PK.

TEAEs leading to death occurred in seven (6%) patients due to COVID-19 disease (n = 3; 0.025 mg, 0.2 mg, and 60 mg), sepsis (n = 1; 5.4 mg), liver injury (n = 1; 50 mg), subdural hematoma (n = 1; 90 mg), and plasma cell myeloma (n = 1; 60 mg expansion cohort). All deaths were considered to be unrelated to ABBV-383 by the investigator.

Overview: AE of Interest

Details of CRS are shown in Table 4 and Appendix Figure A2 (online only). All events of CRS were considered to be related to ABBV-383 by the investigator. The onset of CRS typically occurred on the same day or the day following the first dose of ABBV-383, with a median time to onset of 1 day (overall population: range, 1-7 days; ≥ 40 mg escalation plus expansion cohorts: range, 1-2 days). The median time to resolution was 1 day (range, 1-8 days) in both the overall population and ≥ 40 mg escalation plus expansion cohorts; patients recovered quickly with standard

supportive care measures and/or administration of tocilizumab. Most CRS events were grade 1 or 2 in all dose groups (Table 4). CRS grade ≥ 3 occurred in three (3%) patients at doses ≥ 60 mg (one each at 60 mg [expansion], and 90 mg and 120 mg [escalation]). Serious CRS events occurred in 22 (18%) patients in the overall population, 21 (26%) of which were in the ≥ 40 mg escalation plus expansion cohorts. A single patient in the study (at 40 mg) experienced recurrent CRS after cycle 1 (first event: grade 1, cycle 1 day 1-3; recurrent event: day 70 [cycle 4], 40 mg dose level). In total, 17 (14%) patients, all within the ≥ 40 mg escalation plus expansion cohorts, received tocilizumab.

Serious TEAEs considered to be neurotoxic, as evidenced by the preferred term immune effector cell-associated neurotoxicity, were reported in two patients (60 mg each).

PK and Immunogenicity

The preliminary PK analysis included data from 99 patients. ABBV-383 demonstrated dose-proportional PK at doses between 5.4 mg and 120 mg (Appendix Fig A3, online only). ABBV-383 concentrations from 0.025 mg and 0.075 mg were below the limits of quantification. The half-life ($t_{1/2}$) was approximately 12 days for doses between 5.4 mg and 120 mg, supporting the once every 3 weeks dosing schedule. Preliminary immunogenicity assessment of ABBV-383 indicates a relatively low incidence of immunogenicity with only four out of 76 (5%) evaluable patients treated with ABBV-383 having low-titer ADAs.

Efficacy

Response rates by dose group are shown in Table 5. The ORR and VGPR or better (≥ VGPR) rates for all efficacy-evaluable patients (n = 122) were 57% and 43%,

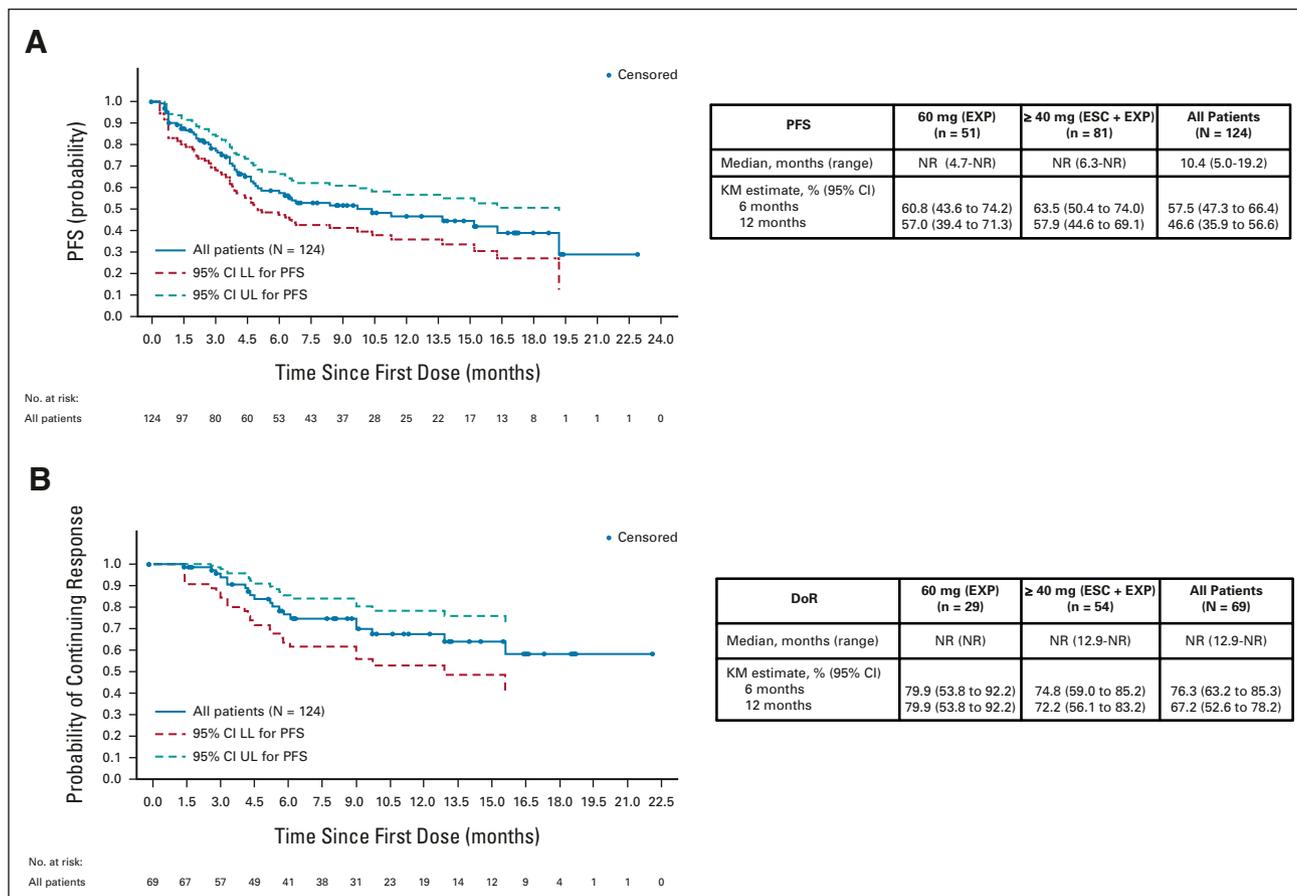


FIG 1. DoR by IMWG criteria and PFS. DoR is for \geq PR. DoR, duration of response; ESC, dose escalation; EXP, dose expansion; IMWG, International Myeloma Working Group; KM, Kaplan-Meier; LL, lower limit; NR, not reached; PFS, progression-free survival; UL, upper limit.

respectively. In the 60 mg expansion cohort ($n = 49$), the ORR and \geq VGPR rates were 59% and 39%, respectively; and in the ≥ 40 mg escalation plus expansion cohorts ($n = 79$) were 68% and 54%, respectively. Of the 11 MRD-evaluable patients with CR or sCR, eight (73%) were MRD-negative ($\leq 10^{-5}$). All five MRD-evaluable patients treated in the ≥ 40 mg escalation plus expansion cohorts achieved MRD-negative CR at $\leq 10^{-6}$ sensitivity threshold by next-generation sequencing. In triple-class refractory patients (defined as refractory to an IMiD, a PI, and an anti-CD38 mAb) overall ($n = 100$), the ≥ 40 mg escalation plus expansion cohorts ($n = 64$), and 60 mg expansion cohort ($n = 41$), the ORRs were 51%, 63%, and 54%, respectively. In patients with high-risk cytogenetics in the ≥ 40 mg escalation plus expansion cohorts ($n = 11$), the ORR, \geq CR (sCR), VGPR, and PR rates were 82%, 27% (18%), 73%, and 9%, respectively. DoR for patients who achieved \geq PR ($n = 69$) is shown in Figure 1A. At the time of the data cutoff, the median DoR had not been reached in the 60 mg expansion ($n = 29$) or the ≥ 40 mg escalation plus expansion cohorts ($n = 54$). The Kaplan-Meier estimate for the 6- and 12-month DoR rate was 79.9% (95% CI, 53.8 to 92.2) and 79.9% (95% CI, 53.8 to 92.2), respectively, for the 60 mg expansion cohort, and 74.8% (95% CI, 59.0 to

85.2) and 72.2% (95% CI, 56.1 to 83.2), respectively, for the ≥ 40 mg escalation plus expansion cohorts. Response over time for patients who achieved \geq PR ($n = 69$) is shown in Appendix Figure A4 (online only). Median PFS was not reached in the ≥ 40 mg escalation plus expansion ($n = 81$) and 60 mg expansion ($n = 51$) cohorts (Fig 1B), and was 10.4 months (range, 5-19.2 months) on the overall population ($N = 124$). Overall, the median duration of follow-up was 10.8 months (range, 0.6-28.2 months) for all treated patients ($N = 124$), 8.2 months (range, 0.6-11.5 months) in the 60 mg expansion cohort ($n = 51$), and 9.6 months (range, 0.6-18.2 months) in the ≥ 40 mg escalation plus expansion cohorts ($n = 81$; Table 2).

DISCUSSION

The results of this first-in-human, phase I study in patients with RRMM demonstrated that the T-BSAb BCMA-targeted therapy ABBV-383 was well tolerated at all doses administered, with a low incidence of grade ≥ 3 hematologic and nonhematologic TEAEs. ABBV-383 was associated with predictable and manageable CRS, without the need to implement step-dosing, and resolution occurred quickly with standard supportive care measures including the

administration of tocilizumab if needed; only 14% of patients received tocilizumab. The majority of CRS events were grade 1 or 2 and resolved in 1 day. PK data indicated a $t_{1/2}$ of approximately 12 days, supporting the extended once every 3 weeks dosing. ABBV-383 also demonstrated a low level of immunogenicity, with ADA formation reported in only 5% of patients. In addition, ABBV-383 showed promising efficacy in the treatment of RRMM with an ORR of 59% observed at 60 mg in the expansion cohort (median follow-up: 8.2 months) and an ORR of 68% observed in the ≥ 40 mg escalation plus expansion cohorts (with a longer median follow-up of 9.6 months). The median 6- and 12-month DoR estimates were $> 72\%$ for both the 60 mg expansion cohort and the ≥ 40 mg escalation plus expansion cohort. The MTD was not reached, and the 60 mg once every 3 weeks dose was selected for dose-expansion on the basis of CRS, plateauing ORR, and PK.

BCMA is an important target for the treatment of RRMM, and several BCMA-targeted therapies have been approved or are in clinical development. These include belantamab mafodotin, CAR-T therapies (eg, idecabtagene vicleucel, and ciltacabtagene autoleucel), as well as the BsAbs CC-93269, REGN5458, teclistamab, and elranatamab. ABBV-383 has similar or improved efficacy in terms of ORRs (59% [60 mg expansion] and 68% [≥ 40 mg escalation plus expansion]) compared with the ADC belantamab mafodotin (32%),²⁰ the CAR-T therapies (61.5%-97%),²¹⁻²⁴ and the

forementioned BsAbs (44%-75%).²⁵⁻²⁸ The tolerability profile of ABBV-383 demonstrated a 57% overall incidence of CRS (73% at ≥ 40 mg) without implementation of priming. CAR-T therapies have reported the following CRS rates: idecabtagene vicleucel, 84%²⁴; ciltacabtagene autoleucel, 95%.²² For BsAbs, overall CRS rate is approximately 70 (eg, CC-93269, 77%²⁶; teclistamab, 72%²⁷; elranatamab, 73%²⁵), which includes lower doses. In addition, this study allowed for the inclusion of patients with diminished renal function as well as patients who received allogeneic transplant in comparison with CAR-T therapy clinical studies. The once every 3 weeks schedule of ABBV-383 was also viewed as convenient in that it may lead to improved compliance from patients as well as minimize the use of hospital resources. Finally, ABBV-383 has off-the-shelf availability, unlike CAR-T therapies, as well as shorter hospitalization time (first 48 hours after initial administration) versus other BCMA and CAR-T therapies.

Limitations of this study involve the small number of patients enrolled in the dose escalation cohorts. Efforts are ongoing to determine the optimal dose regimen for ABBV-383 with lower doses being explored. ABBV-383 doses of 60 mg once every 3 weeks as well as 40 mg once every 3 weeks have been selected for further dose exploration and optimal-dose selection. The safety and efficacy of ABBV-383 will be investigated further in this ongoing phase I study.

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[trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html](https://www.clinicaltrials.gov/ct2/show/study/NCT03833333).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**A Phase I First-In-Human Study of ABBV-383, a B-Cell Maturation Antigen × CD3 Bispecific T-Cell Redirecting Antibody, in Patients With Relapsed/Refractory Multiple Myeloma**

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APPENDIX 1. METHODS

Study Treatment

ABBV-383 is administered by intravenous (IV) infusion over 1-2 hours at a fixed dose once every 3 weeks. If no infusion reactions occur during the first dose, the duration of the infusion for subsequent doses can be reduced to 1 hour. ABBV-383 cannot be administered over a period < 1 hour. Patients are also routinely premedicated with diphenhydramine

25-50 mg IV (once on day 1) or equivalent, oral acetaminophen 650-1,000 mg (once on day 1), and ranitidine 150 mg oral/IV (once on day 1) or equivalent, 15-60 minutes before the ABBV-383 infusion (once every 3 weeks) to reduce the risk and severity of hypersensitivity reactions commonly observed with monoclonal antibody therapy. Patients can also be premedicated with tocilizumab 8 mg/kg IV (once on day 1) at the discretion of the investigator or according to the institution's guidelines prior to the administration of ABBV-383 (once every 3 weeks).

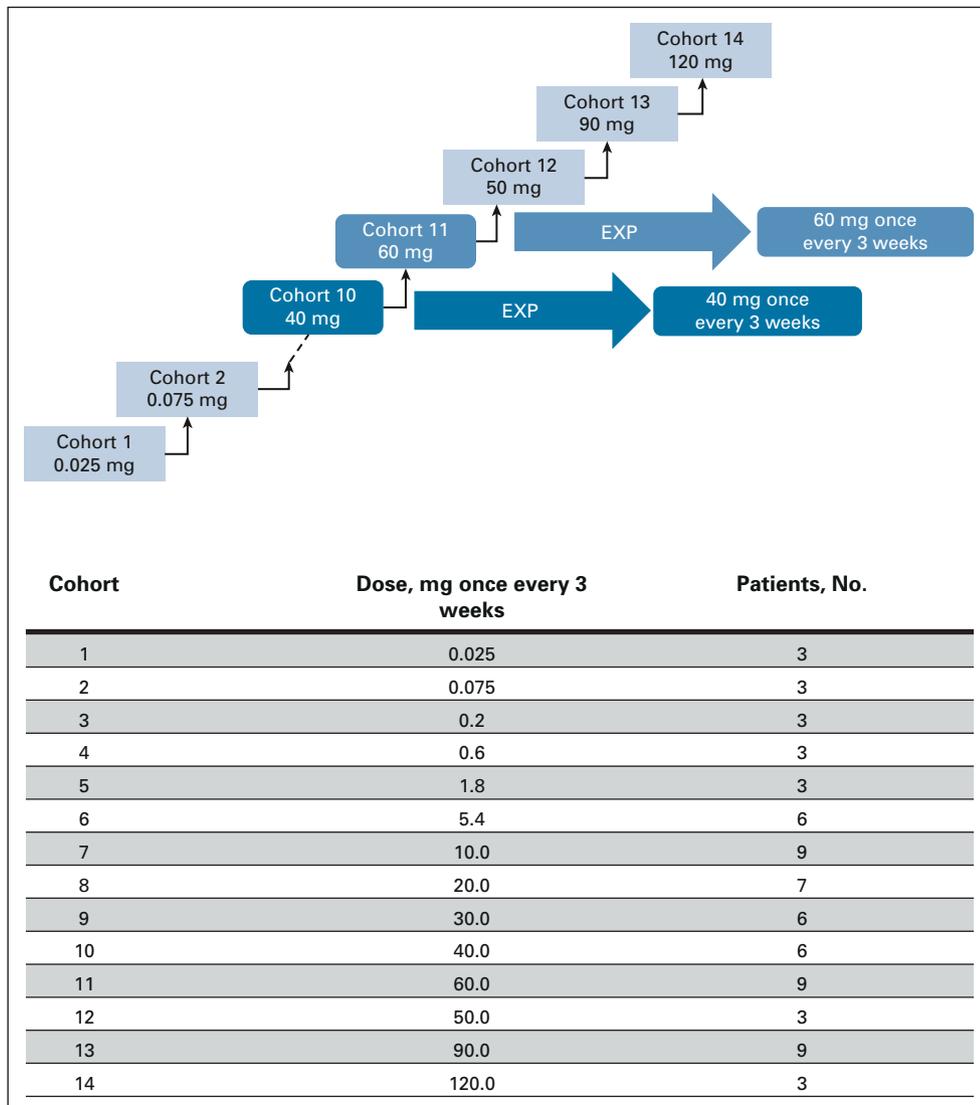


FIG A1. Study design and dose-expansion cohorts. Dose escalation study using a 3 + 3 design with backfilling. EXP, dose expansion.

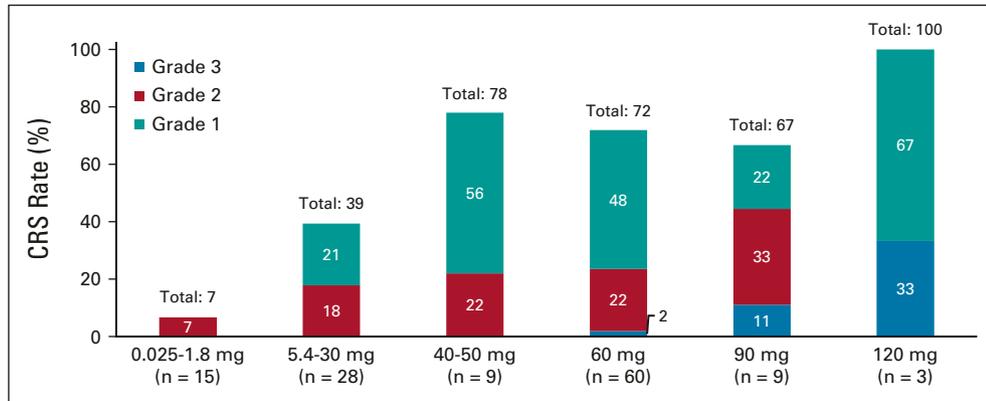


FIG A2. CRS overview: grade and dose. CRS, cytokine release syndrome; ESC, dose escalation; EXP, dose expansion.

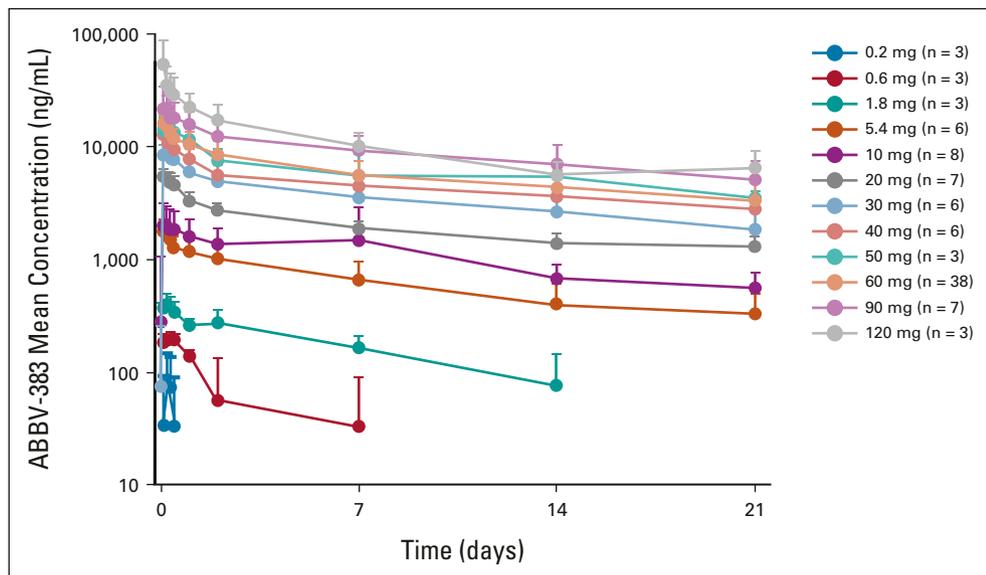


FIG A3. Clinical pharmacokinetics. Serum concentrations for 0.025 mg (n = 3) and 0.075 mg (n = 3) were below the limit of quantitation at all time points.

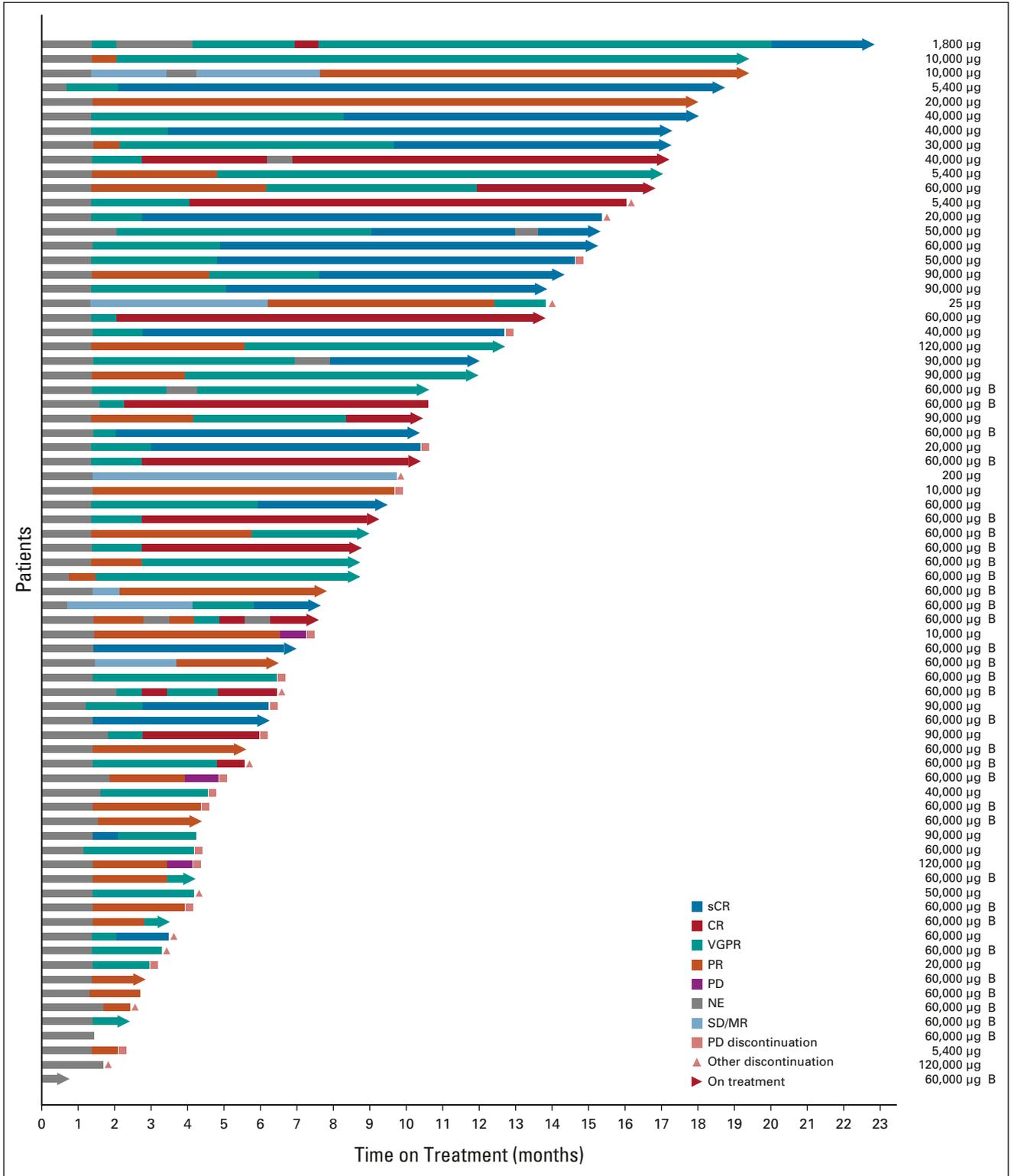


FIG A4. Response over time in patients with \geq PR. CR, complete response; MR, minor response; NE, not evaluable; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

TABLE A1. Eligibility Criteria

Key inclusion criteria:

Age \geq 18 years \geq three prior lines of therapy with exposure to a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody (ie, daratumumab)

Must not be candidates for treatment regimens known to provide clinical benefit in MM

Note: the number of prior lines of therapy will be determined according to the guidelines provided in the study by Rajkumar et al.²⁹ There is no maximum number of prior lines of therapyECOG PS score of \leq 2Adequate bone marrow function (ANC \geq 1,000/mm³, platelets \geq 50,000/mm³, hemoglobin \geq 8.0 g/dL)

Transfusion and/or growth factor support is permitted before assessment, but neutrophils, platelets, and hemoglobin must be stable for at least 72 hours after transfusion and/or growth factor administration before screening for the patient to be eligible

eGFR \geq 30 mL/minute as estimated by the Modification of Diet in Renal Disease formulaTotal bilirubin \leq 1.5 \times ULN (excluding a known diagnosis of Gilbert's syndrome, in which case bilirubin must be $<$ 3 \times ULN) and AST and ALT \leq 3 \times ULN
Serum calcium (corrected for albumin) at or below the ULN range (patient may enroll in the setting of hypercalcemia at screening IF hypercalcemia resolves with standard treatment by cycle 1 day 1) before study therapy initiationCorrected serum calcium (mg/dL) = measured serum calcium (mg/dL) + 0.8 \times (4.0 – serum albumin [g/dL])Measurable disease as defined by \geq 1 of the following:Serum M-protein \geq 0.5 g/dL (\geq 5 g/L)Urine M-protein \geq 200 mg/24 hoursSerum FLC assay: involved FLC level \geq 10 mg/dL (\geq 100 mg/L) and an abnormal serum FLC ratio ($<$ 0.26 or $>$ 1.65)

Confirmed evidence of relapse/progression from the immediately prior MM therapy, or patient is relapsed/refractory to the immediately prior MM therapy

Patient consents to a fresh pretreatment bone marrow tumor biopsy or has adequate archival bone marrow tumor tissue that was collected within 6 months before screening and without intervening treatment

Key exclusion criteria:

Diagnosed or treated for another malignancy within \leq 3 years of enrollment (excluding basal cell or squamous cell carcinoma of the skin, in situ malignancy, low-risk prostate carcinoma after curative therapy, or complete resection/curative therapy of an advanced malignancy)History of CNS involvement by their myeloma, grade \geq 3 peripheral neuropathy, plasma cell leukemia, POEMS syndrome, or amyloidosisReceived another investigational drug \leq 21 days of enrollment

Received BCMA-targeted therapy (non-BCMA targets were not excluded)

Received an autologous stem-cell transplant (\leq 12 weeks) or an allogeneic stem-cell transplant (\leq 1 year) before first dose of study drug treatmentReceived any therapy to treat cancer (including radiation, chemotherapy, biologics, cellular therapies, and/or steroids at doses $>$ 20 mg dexamethasone or equivalent) or undergone a major surgical procedure \leq 21 days, or within 5 half-lives of an anticancer drug, before the first dose of study treatment, whichever is shorterKnown active infection grade \geq 2 requiring anti-infective treatment. Upon completion of anti-infectives and resolution to grade \leq 1, the patient is considered eligible for the study from an infection standpoint. For patients who have active SARS-CoV-2 infection:

If the subject has signs/symptoms suggestive of SARS-CoV-2 infection, he/she should undergo molecular (eg, polymerase chain reaction) testing to confirm SARS-CoV-2 infection. Patients who meet SARS-CoV-2 infection criteria must be screen failed but will be allowed to rescreen

Confirmed positive test results for HIV, or patients with chronic or active infection with HBV or HCV

Patients who have a history of HBV or HCV who have documented cures (HBV: hepatitis B surface antigen–negative; HCV: undetectable HCV ribonucleic acid 24 weeks after the EOT) may enroll

Major cardiac abnormalities such as, but not limited to, the following: uncontrolled angina or unstable life-threatening arrhythmias, history of myocardial infarction \leq 12 weeks before screening, class \geq 3 New York Heart Association congestive heart failure, severe cardiac insufficiency, or persistent QTc prolongation ($>$ 480 ms, QTc per Fridericia's formula)Unresolved AEs \geq grade 2 (NCI CTCAE, version 5.0) from prior anticancer therapy except for:

Alopecia

Peripheral neuropathy (\geq grade 3 will be excluded)

Anemia or thrombocytopenia (anemia must be grade 3, and thrombocytopenia must be grade 4 to trigger exclusion, grade 3 with symptoms or bleeding, respectively, or return within 72 hours despite transfusion support)

Irreversible toxicity not reasonably expected to be exacerbated by any of the investigational products may be included (eg, hearing loss) after consultation with the study medical monitor

Abbreviations: ANC, absolute neutrophil count; BCMA, B-cell maturation antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; EOT, end-of-treatment; FLC, free light chain; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MM, multiple myeloma; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; POEMS, polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes; QTc, QT interval corrected for heart rate; ULN, upper limit of normal.