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

Anita D'Souza, MD1; Nina Shah, MD2; Cesar Rodriguez, MD3; Peter M. Voorhees, MD4; Katja Weisel, MD5; Orlando F. Bueno, MD, PhD6; Rajvineeth K. Pothacamury, MD6; Kevin J. Freise, PhD6; Susan Yue, MD6; Jeremy A. Ross, PhD6; Akshanth R. Polepally, PhD6; Chetasi Talati, MD6; Shane Lee, MS6; Ziyi Jin, MS6; Ben Buelow, MD, PhD7; Ravi Vij, MD8; and Shaji Kumar, MD9

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) 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 (intrapatient 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) 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 mAbs3 and a median OS of 5.1-11.5 months in patients who are double or triple/quadruple refractory to PIs and IMiDs.3,4 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.5 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...
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 (≥ 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 very good partial response rate of 54% were reported at the therapeutic doses of ≥ 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.

METHODS

Study Design
To our knowledge, this study was 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.

Patient Eligibility
Full eligibility criteria are listed in the Appendix Table A1 (online only). Briefly, patients (age ≥ 18 years) with RRMM (≥ three prior lines of therapy that included a PI, an IMiD, and an anti-CD38 mAb), estimated glomerular filtration rate ≥ 30 mL/min as calculated by the Modification of Diet in Renal Disease formula, and Eastern Cooperative Oncology Group performance status (ECOG PS) score ≤ 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 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 intrapatient 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 intrapatient 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 < two 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, 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 (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
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 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 refractoryd | 45 (88) | 68 (84) | 104 (84) |
| Triple-class exposed | 50 (98) | 80 (99) | 123 (99) |
| Triple-class refractorye | 43 (84) | 66 (81) | 102 (82) |
| Penta-class exposed | 45 (88) | 74 (91) | 113 (91) |
| Penta-class refractoryf | 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.
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 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.
### Table 3. TEAEs

| TEAE | 60 mg EXP (n = 51) | ≥ 40 mg ESC + EXP (n = 81) | All Patients (N = 124*) |
|------|--------------------|-----------------------------|-------------------------|
| 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

| Category | 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. (%) | | | | | | |
| Neutropeniaa | 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) |
| Thrombocytopeniac | 13 (25) | 5 (10) | 20 (25) | 9 (11) | 29 (23) | 15 (12) |
| Lymphopeniad | 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.
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 platelet 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 (t1/2) 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%,
respectively. In the 60 mg expansion cohort (n = 49), the ORR and \(\geq\) VGPR rates were 59% and 39%, respectively; and in the \(\geq\) 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 (\#10–5). All five MRD-evaluable patients treated in the \(\geq\) 40 mg escalation plus expansion cohorts achieved MRD-negative CR at \#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 \(\geq\) 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 \(\geq\) 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 \(\geq\) 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 \(\geq\) 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 \(\geq\) 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 \(\geq\) 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 \(\geq\) 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 t½ 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 aforementioned 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 allogenic 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 BCMAs 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.
trials/career-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

**AUTHOR CONTRIBUTIONS**

**Conception and design:** Nina Shah, Cesar Rodriguez, Peter M. Voorhees, Katja Weisel, Rajvinee K. Pothacumary, Kevin J. Freise, Akshanth R. Polepally, Chetasi Talati, Ziyi Jin, Ben Buelow, Shaji Kumar

**Administrative support:** Ben Buelow

**Provision of study materials or patients:** Anita D’Souza, Peter M. Voorhees, Katja Weisel, Orlando F. Bueno

**Collection and assembly of data:** Anita D’Souza, Nina Shah, Cesar Rodriguez, Peter M. Voorhees, Katja Weisel, Orlando F. Bueno

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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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AUTHORS

Anita D’Souza
Consulting or Advisory Role: Pfizer, Janssen, Akcea Therapeutics, Bristol Myers Squibb/Celgene, Prothera
Research Funding: Takeda (Inst), Sanofi (Inst), TeneoBio (Inst), Prothera (Inst), Caelum Biosciences (Inst), Janssen Oncology, Regeneron, AbbVie,
Travel, Accommodations, Expenses: Imbrium Therapeutics

Nina Shah
Employment: AstraZeneca
Stock and Other Ownership Interests: AstraZeneca
Consulting or Advisory Role: Indapta Therapeutics, Sanofi, Oncoproteins, Karyopharm Therapeutics, Genentech/AbbVie, GlaxoSmithKline, Amgen, CareDX
Research Funding: Janssen Oncology, Regeneron, AbbVie
Travel, Accommodations, Expenses: Imbrium Therapeutics

Cesar Rodriguez
Consulting or Advisory Role: Janssen, Artiva
Speakers’ Bureau: Bristol-Myers Squibb/Celgene, Sanofi

Peter M. Voorhees
Consulting or Advisory Role: Oncoproteins, Karyopharm Therapeutics, Bristol Myers Squibb, Secura Bio, Pfizer, Sanofi, Janssen, GlaxoSmithKline
Research Funding: AbbVie (Inst), Janssen (Inst), GlaxoSmithKline (Inst), TeneoBio (Inst)
Travel, Accommodations, Expenses: Sanofi

Uncompensated Relationships: GlaxoSmithKline

Katja Weisel
Honoraria: Amgen, Bristol Myers Squibb, Janssen-Cilag, GlaxoSmithKline, Adaptive Biotechnologies, Karyopharm Therapeutics, Takeda, Sanofi, AbbVie, GlaxoSmithKline, Novartis, Pfizer, Amgen (Inst), Bristol Myers Squibb/Celgene (Inst), Celgene, Janssen (Inst), GlaxoSmithKline (Inst), Oncoproteins, Roche, Sanofi (Inst)
Consulting or Advisory Role: Amgen, Adaptive Biotechnologies, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen-Cilag, Karyopharm Therapeutics, Sanofi, Takeda, Oncoproteins, Roche
Research Funding: Amgen (Inst), Celgene (Inst), Sanofi (Inst), Janssen-Cilag (Inst), Bristol Myers Squibb/Celgene (Inst), GlaxoSmithKline (Inst)
Travel, Accommodations, Expenses: Amgen, Celgene, Bristol Myers Squibb, Janssen-Cilag, GlaxoSmithKline, Takeda

Orlando F. Bueno
Employment: AbbVie
Stock and Other Ownership Interests: AbbVie
Research Funding: AbbVie
Travel, Accommodations, Expenses: AbbVie

Rajvineeth K. Pothacamury
Employment: AbbVie
Stock and Other Ownership Interests: AbbVie

Kevin J. Freise
Employment: AbbVie
Stock and Other Ownership Interests: AbbVie

Susan Yue
Employment: AbbVie, Atara Biotherapeutics
Stock and Other Ownership Interests: AbbVie, Atara Biotherapeutics

Jeremy A. Ross
Employment: AbbVie
Stock and Other Ownership Interests: AbbVie

Aksharth R. Polepally
Employment: AbbVie
Stock and Other Ownership Interests: AbbVie

Patents, Royalties, Other Intellectual Property: pending patent application

Chetasi Talati
Employment: AbbVie
Stock and Other Ownership Interests: AbbVie

Shane Lee
Employment: AbbVie/Pharmacyclics, Regeneron
Stock and Other Ownership Interests: AbbVie/Pharmacyclics

Ziyi Jin
Employment: AbbVie
Stock and Other Ownership Interests: AbbVie

Ben Buelow
Employment: Teneobio, Ancora Biotech, Inc
Leadership: Teneobio, Ancora Biotech, Inc
Stock and Other Ownership Interests: Teneobio, Ancora Biotech, Inc
Patents, Royalties, Other Intellectual Property: Co-patent holder of some Teneobio patents

Ravi Vij
Consulting or Advisory Role: Sanofi, CareDX, Legend Biotech, GlaxoSmithKline, Oncoproteins, Harpoon, Adaptive Biotechnologies, Pfizer, Bristol Myers Squibb/Celgene, Research Funding: Takeda (Inst), Bristol Myers Squibb (Inst), Sanofi (Inst)
Travel, Accommodations, Expenses: Celgene, Bristol Myers Squibb, Sanofi, Janssen, Dava Oncology, Karyopharm Therapeutics, Amgen, Takeda, AbbVie

Shaji Kumar
Honoraria: Beigene, GLH Pharma, Secura Bio
Consulting or Advisory Role: Takeda (Inst), Janssen Oncology (Inst), Amgen (Inst), AbbVie (Inst), Celgene (Inst), Genentech/Roche (Inst), AbbVie (Inst), Oncoproteins, Kite, a Gilead company (Inst), Genencetrix, Molecular Partners, Bluebird Bio
Research Funding: Celgene (Inst), Takeda (Inst), AbbVie (Inst), Novartis (Inst), Sanofi (Inst), Janssen Oncology (Inst), Merck (Inst), Kite, a Gilead company (Inst), Medimmune (Inst), Roche/Genentech (Inst), TeneoBio (Inst), CARsgen Therapeutics (Inst)

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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 650-1000 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).

Cohorts and Dose Levels:

| Cohort | Dose, mg once every 3 weeks | Patients, No. |
|--------|-----------------------------|---------------|
| 1      | 0.025                       | 3             |
| 2      | 0.075                       | 3             |
| 3      | 0.2                         | 3             |
| 4      | 0.6                         | 3             |
| 5      | 1.8                         | 3             |
| 6      | 5.4                         | 6             |
| 7      | 10.0                        | 9             |
| 8      | 20.0                        | 7             |
| 9      | 30.0                        | 6             |
| 10     | 40.0                        | 6             |
| 11     | 60.0                        | 9             |
| 12     | 50.0                        | 3             |
| 13     | 90.0                        | 9             |
| 14     | 120.0                       | 3             |

**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 ≥ 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 ≥ 18 years
- ≥ three prior lines of therapy
- 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 therapy

**ECOG PS score of ≤ 2**

- Adequate bone marrow function (ANC ≥ 1,000/mm³, platelets ≥ 50,000/mm³, hemoglobin ≥ 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 ≥ 30 ml/minute as estimated by the Modification of Diet in Renal Disease formula
- Total bilirubin ≤ 1.5 × ULN (excluding a known diagnosis of Gilbert’s syndrome, in which case bilirubin must be < 3 × ULN) and AST and ALT ≤ 3 × 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 initiation)
- Corrected serum calcium (mg/dL) = measured serum calcium (mg/dL) + 0.8 × (4.0 – serum albumin [g/dL])

**Measurable disease as defined by ≥ 1 of the following:**

- Serum M-protein ≥ 0.5 g/dL (≥ 5 g/L)
- Urine M-protein ≥ 200 mg/24 hours
- Serum FLC assay: involved FLC level ≥ 10 mg/dL (≥ 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 ≤ 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 ≥ 3 peripheral neuropathy, plasma cell leukemia, POEMS syndrome, or amyloidosis
- Received another investigational drug ≤ 21 days of enrollment
- Received BCMA-targeted therapy (non-BCMA targets were not excluded)
- Received an autologous stem-cell transplant (≤ 12 weeks) or an allogeneic stem-cell transplant (≤ 1 year) before first dose of study drug treatment
- Received 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 ≤ 21 days, or within 5 half-lives of an anticancer drug, before the first dose of study treatment, whichever is shorter
- Known active infection grade ≥ 2 requiring anti-infective treatment. Upon completion of anti-infectives and resolution to grade ≤ 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 ≤ 12 weeks before screening, class ≥ 3 New York Heart Association congestive heart failure, severe cardiac insufficiency, or persistent QTc prolongation (≥ 480 ms, QTc per Fridericia’s formula)
- Unresolved AEs ≥ grade 2 (NCI CTCAE, version 5.0) from prior anticancer therapy except for:
  - Alopecia
  - Peripheral neuropathy (≥ 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.