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# Anti–B-Cell Maturation Antigen BiTE Molecule AMG 420 Induces Responses in Multiple Myeloma

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abstract

**PURPOSE** The anti–B-cell maturation antigen BiTE molecule AMG 420 was assessed in patients with relapsed/refractory multiple myeloma.

**PATIENTS AND METHODS** In this first-in-human study, up to 10 cycles of AMG 420 were given (4-week infusions/6-week cycles). Patients had progression after ≥ 2 lines of prior therapy and no extramedullary disease. Minimal residual disease (MRD) response was defined as < 1 tumor cell/$10^4$ bone marrow cells by flow cytometry.

**RESULTS** Forty-two patients received AMG 420 at 0.2-800 μg/d. Median age was 65 years, and median disease duration was 5.2 years. Median exposure was 1 cycle (range, 1-10 cycles) and 7 cycles (range, 1-10 cycles) for responders. Patients discontinued for disease progression (n = 25), adverse events (AEs; n = 7), death (n = 4), completion of 10 cycles (n = 3), and consent withdrawal (n = 1). Two patients remain on treatment. There were 2 nontreatment-related deaths from AEs, influenza/aspergillosis and adenovirus-related hepatitis. Serious AEs (n = 20; 48%) included infections (n = 14) and polyneuropathy (n = 2); treatment-related serious AEs included 2 grade 3 polyneuropathies and 1 grade 3 edema. There were no grade ≥ 3 CNS toxicities or anti-AMG 420 antibodies. In this study, 800 μg/d was considered to not be tolerable because of 1 instance each of grade 3 cytokine release syndrome and grade 3 polyneuropathy, both of which resolved. The overall response rate was 31% (n = 13 of 42). At the maximum tolerated dose (MTD) of 400 μg/d, the response rate was 70% (n = 7 of 10). Of these, five patients experienced MRD-negative complete responses, and 1 had a partial response, and 1 had a very good partial response; all 7 patients responded during the first cycle, and some responses lasted > 1 year.

**CONCLUSION** In this study of AMG 420 in patients with relapsed/refractory multiple myeloma, the response rate was 70%, including 50% MRD-negative complete responses, at 400 μg/d, the MTD for this study.

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## INTRODUCTION

Despite numerous new therapies approved over the past several years, multiple myeloma is not considered curable, with relapse inevitably part of the expected disease course.[1] One promising target for multiple myeloma is B-cell maturation antigen (BCMA), or TNFRSF17, which is expressed on multiple myeloma cells, plasma cells, and mature B cells[2-5] and required for long-term survival of plasma cells.[6] There are several anti-BCMA investigational agents, such as chimeric antigen receptor T (CAR-T) cells,[7-15] bispecific antibody-based molecules,[16,17] and antibody-drug conjugates.[18] Blinatumomab, a BiTE (bispecific T-cell engager) molecule that engages T cells to cells that express CD19, has been shown to be effective in relapsed/refractory acute lymphoblastic leukemia.[19] AMG 420, formerly BI 836909, is an investigational BiTE molecule that binds BCMA on target cells, resulting in T-cell–mediated lysis of BCMA-positive cells, at least in part through a Fas-mediated mechanism.[20,21] We describe here results of a first-in-human dose escalation trial in which patients with relapsed/refractory multiple myeloma with disease progression after ≥ 2 lines of therapy, including proteasome inhibitors and immunomodulatory drugs (IMiDs), received up to 10 cycles of AMG 420.[16]

## PATIENTS AND METHODS

### Objectives

Primary objectives of this study of AMG 420 in relapsed/refractory multiple myeloma were to determine

ASSOCIATED CONTENT

Appendix

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

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the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs). Secondary objectives included the assessment of safety using Common Terminology Criteria for Adverse Events (version 4.03; CTCAE), immunogenicity, antitumor activity, and pharmacokinetics.

### End Points

The primary end points were DLT and MTD, which was defined as the highest dose at which ≤ 1 of 6 patients develops a DLT. Secondary end points included response per International Myeloma Working Group 2006 (adapted from Durie et al[22] and Kyle and Rajkumar[23]), including the objective response rate (ORR; partial response [PR], very good PR [VGPR], complete response [CR], minimal residual disease [MRD]–negative CR) and duration of response. Evaluable patients had at least 1 postbaseline response assessment. MRD was defined for this study as $< 1$ tumor cell/$10^4$ normal cells in the bone marrow per central laboratory flow cytometry using antibodies to cytIgλ, cytIgκ, CD19, CD56, CD138, CD38, and CD45, and was confirmed morphologically. Another secondary end point was AMG 420 concentration at steady state.

### Eligible Patients

Eligible patients were ≥ 18 years old and had relapsed/refractory multiple myeloma with progression after ≥ 2 prior treatment lines (including both ≥ 1 proteasome inhibitors and ≥ 1 IMiDs). Major exclusion criteria were plasma cell leukemia, extramedullary relapse, known CNS involvement, prior allogeneic stem-cell transplant, significant comorbidities, active infection that required treatment, and active autoimmune disease.

### Study Design

This was a first-in-human, phase I, dose escalation, multicenter study of AMG 420 given for up to 10 cycles, with each 6-week cycle including 4 weeks of continuous intravenous administration followed by 2 weeks off treatment (Appendix Fig A1, online only). Study procedures were approved by institutional review boards at each site, and all patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

At the beginning of each cycle, required premedications included glucocorticoids (16 mg dexamethasone or equivalent), antihistamine, and paracetamol to minimize any infusion reaction or cytokine release syndrome (CRS). If the first cycle was well tolerated, pretreatment with glucocorticoids could subsequently be reduced/omitted. Treatment was for up to 5 cycles or until disease progression/additional anticancer treatment, toxicity, withdrawal of consent, or investigator decision. Five more cycles could be given for benefit per investigator for a total of up to 10 cycles. Single-patient cohorts (0.2, 0.4, 0.8, 1.6 μg/d) were followed by cohorts of 3-6 patients (3.2, 6.5, 13, 25, 50, 100, 200, 400, 800 μg/d). Once the MTD was reached, up to 6 additional patients could be enrolled in the cohort expansion. The first patient enrolled on August 26, 2015.

### Statistical Methods and Analysis Sets

Data from this ongoing study are reported as of April 8, 2019. Data from patients with DLTs, ORRs, and MRD were summarized by descriptive statistics. For MTD determination, 4 patients were replaced (3 treated ≤ 15 days with no DLTs and 1 because of an inclusion violation that was the result of extramedullary disease). One patient died 1 day after responding (liver failure) and was not included in response duration calculations. Cell surface BCMA expression was measured by flow cytometry with mean fluorescence intensity/molecules of equivalent soluble fluorochrome. All biomarker analyses were descriptive in nature (no statistical comparisons conducted).

## RESULTS

### Patient Baseline Characteristics

Forty-two patients were included in the analysis (median age, 65 years; 64% male; Table 1). The median disease duration was 5.2 years, with 33% of patients having high-risk cytogenetics (as assessed per guidelines by Sonneveld et al[24]; cytogenetics were also assessed per Rajkumar[25] 2012 guidelines). The median number of prior therapies was 5 as assessed per investigator at study entry and 3.5 in post hoc determination per Rajkumar et al[26] 2015 guidelines, with 29% having received prior daratumumab, 10% prior elotuzumab, and 86% prior autologous stem-cell transplant.

### Patient Disposition, Exposure, and Pharmacokinetics

Of the 42 patients, 3 completed 10 cycles of AMG 420, 2 are ongoing, 25 discontinued because of disease progression and 7 because of adverse events (AEs; including 3 port/line infections, 1 biliary obstruction, and 3 DLT), 4 died, and 1 withdrew consent (Table 2). Eight patients completed 5 cycles and subsequently, either completed 10 cycles (n = 3), discontinued for progressive disease (n = 3), or are still on treatment (n = 2). Patients were treated for a median of 1 cycle (range, 1-10 cycles); responders were treated for a median of 7 cycles (range, 1-10 cycles). Two patients had dose reductions. Dose was decreased in 1 patient from 400 to 200 μg/d temporarily per investigator after another patient at that site died as a result of liver failure; the patient was subsequently re-escalated to 400 μg/d. Dose was decreased in 1 other patient from 800 to 400 μg/d because of weight loss. On average, free AMG 420 concentrations increased with increasing dose (Fig 1A).

### Safety

***DLTs and CRS.*** In this study, 800 μg/day was determined to not be tolerable because 2 of 3 patients experienced DLTs. One patient had grade 3 CRS within 1 day of initiating treatment, with fever, hypertension, tachycardia, and

**TABLE 1.** Baseline Characteristics

| Characteristic | Value |
|---|---|
| No. of patients | 42 |
| Male, No. (%) | 27 (64) |
| Median age, years (range) | 65 (39-79) |
| ECOG performance status, % | |
| 0 | 57 |
| 1 | 40 |
| 2 | 2 |
| Median disease duration, years (range) | 5.2 (1.3-20.0) |
| Cytogenetics per IMWG 2016 guidelines,[24] % | |
| Standard | 67 |
| High | 33 |
| Cytogenetics per Rajkumar[25] 2012 guidelines, % | |
| Standard | 60 |
| Intermediate | 29 |
| High | 12 |
| Median plasma cells at baseline, % (range) | 18 (0-95) |
| Prior lines of therapy as assessed at study entry per investigator, median (range) | 5 (2-14) |
| Prior lines of therapy as assessed post hoc per Rajkumar[26] 2015 guidelines, median (range) | 3.5 (1.0-10.0) |
| Prior therapies, median (range)[a] | 7 (3-14) |
| Prior daratumumab,[b] No. (%) | 12 (29) |
| Prior elotuzumab, No. (%) | 4 (10) |
| Prior autologous stem-cell transplant, No. (%) | 36 (86) |
| Refractory to past therapies, median (range) | 1 (0-10) |
| Refractory to which drug type, % | |
| Immunomodulatory drug | 48 |
| Proteasome inhibitor | 38 |
| Immunomodulatory drug and proteasome inhibitor | 36 |
| Refractory to daratumumab, % | 21 |
| Refractory to elotuzumab, % | 7 |

NOTE. In total, 48 patients were screened and consented, and 42 were treated. Of the 6 patients not treated, 5 had screen failures, and 1 withdrew consent.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IMWG, International Myeloma Working Group.

[a]A given therapy could be counted as a line more than once (ie, different dose/schedule after intervening therapies).

[b]Past daratumumab use became more prevalent as the study enrolled. Of the 12 patients who received daratumumab, 1 started the study in 2016, 3 in 2017, and 8 in 2018.

retrograde amnesia; symptoms resolved after discontinuing the study drug and being retreated with premedications. Another patient had grade 2 peripheral polyneuropathy that started 1 week after initiating treatment, which increased in severity to grade 3 by day 15 and required hospitalization. Subsequently, a patient in the 400 μg/d cohort expansion had baseline grade 1 peripheral polyneuropathy, which worsened to grade 3 by day 30; after 3 weeks, the polyneuropathy gradually improved and returned to baseline by day 86 (week 12). Both patients with polyneuropathy improved, with 1 experiencing complete resolution in 2 months and the other returning to baseline polyneuropathy (grade 1) in 3 months (Appendix Table A1, online only). Both patients had responses in the first 4 weeks of the study, with M-protein decreases of 58% and 79%, respectively.

Patients with CRS (16 of 42, including 2 grade 2 and 1 grade 3) were generally treated supportively with glucocorticoids, antihistamines, and paracetamol; some patients received additional analgesics (meperidine, dipyrone, ibuprofen, hydromorphone, fentanyl, tramadol). One patient with CTCAE grade 2 CRS received tocilizumab. AMG 420 was discontinued because of grade 3 CRS (the previously discussed DLT); all other patients continued treatment as before.

***Other Safety.*** Of the 4 deaths in the study, 2 were a result of AEs, neither treatment-related, and 2 a result of disease progression. For the deaths from AEs, 1 patient in the 50 μg/d cohort (with 3 prior lines of treatment, including transplantation) died as a result of acute respiratory distress that was the result of concurrent influenza and aspergillosis that started after the last AMG 420 infusion. A patient in the 400 μg/d cohort (with 5 prior lines of treatment) died as a result of fulminant hepatitis related to adenovirus infection; this patient previously received tocilizumab for CRS. Of the 2 patients who died as a result of disease progression, 1 developed grade 3 edema/acute respiratory failure; it was subsequently found that this patient had extramedullary disease at study entry in violation of eligibility criteria. Another patient died as a result of disease progression after treatment for left ventricular failure deemed unrelated to study treatment.

Of those with serious AEs (SAEs; n = 20; 48%), the most common SAEs were infection (n = 14) and polyneuropathy (n = 2). Three patients experienced treatment-related SAEs, including 2 grade 3 polyneuropathies and the 1 grade 3 edema (Table 3). No grade ≥ 3 CNS toxicities were observed. Peripheral neurologic AEs were grade 1 and 2 and nonspecific (eg, headache, fatigue) except for 1 grade 3 asthenia and the 2 grade 3 peripheral polyneuropathies. No anti-AMG 420 antibodies were detected up to the maximum dose of 800 μg/d.

Five patients experienced elevated hepatic enzymes (AST and/or ALT > 3 times the upper limit of normal) while on treatment, 1 in the 200 μg/d cohort and 4 in the 400 μg/d cohort (1 of whom had elevated hepatic enzymes at baseline). One patient in the 400 μg/d cohort died as a result of hepatic failure that was likely the result of adenovirus infection, with coagulopathy (international normalized ratio > 200-fold), elevated hepatic enzymes > 80- to > 200-fold, and adenovirus serum titer of $10^9$/L (not

**TABLE 2.** Patient Disposition and Exposure

| Disposition and Exposure | No. (%) |
|---|---|
| No. of patients | 42 |
| Reason for discontinuation of AMG 420 | |
| Progressive disease (per IMWG 2006) | 25 (60) |
| AEs, including 3 DLTs[a] | 7 (17) |
| Death[b] | 4 (10) |
| Completed 10 cycles[c] | 3 (7) |
| Withdrew consent | 1 (2) |
| Exposure, No. of cycles started | |
| All | |
| Mean (standard deviation) | 2.8 (2.9) |
| Median (range) | 1 (1-10) |
| Responders[d] | |
| Mean (standard deviation) | 6.3 (3.4) |
| Median (range) | 7 (1-10) |

NOTE. As of April 8, 2019. Two patients are ongoing on treatment.

Abbreviations: AE, adverse event; DLT, dose-limiting toxicity; IMWG, International Myeloma Working Group.

[a]AEs that led to discontinuation were line/port infections (n = 3); biliary obstruction; and the DLTs of peripheral polyneuropathy (n = 2) and cytokine release syndrome (n = 1).

[b]Causes of death were disease progression for 2 patients and AEs for 2 patients (aspergillosis/influenza in 1 and fulminant hepatitis related to adenovirus infection in the other). Although death occurred 1-10 days after last treatment, death was deemed the proximal cause of discontinuation.

[c]After the first 5 cycles, 5 more cycles could be given for perceived benefit. Eight patients completed 5 cycles and subsequently either completed 10 cycles (n = 3), discontinued for progressive disease (n = 3), or were still on treatment as of data cutoff (n = 2).

[d]Includes the 2 patients with treatment ongoing.

treatment related); the grade 4 hepatic enzyme elevation started day 29. Because enrollment of new patients was held while responding to regulatory questions with regard to this patient and an additional study of AMG 420 was being initiated, it was decided to halt enrollment after this patient for a total of 10 patients at 400 μg/d. The onset of hepatic enzyme elevations for the 4 patients with self-limited AST/ALT elevations ranged from day 1 to day 3 and resolved by day 4-17. Except for 1 grade 3 increase in AST, all other increases were grade 2. Other than the patient who died as a result of hepatic failure, none of the other patients had underlying AEs of obvious hepatic etiology. The 4 patients with reversible hepatic enzyme elevations had coincident CRS managed with corticosteroids; the patient who developed liver failure had CRS treated with corticosteroids and tocilizumab earlier in cycle 1.

## Efficacy

During dose escalation, responses were evident starting at 6.5 μg/d (1 CR at this dose). There was 1 PR at 50 μg/d, a CR at 100 μg/d, and an MRD-negative CR at 200 μg/d. Efficacy became most apparent at 400 μg/d (Figs 1B and 1C; Appendix Fig A2, online only). At 400 μg/d, 7 (70%) of 10 patients responded, including 5 MRD-negative CRs, 1 VGPR, and 1 PR. Thus, at the dose of 400 μg/d, the ORR was 70% (95% CI, 34.8% to 93.3%). The depth of responses observed at the 400 μg/d dose was related to the free AMG 420 concentrations achieved in these patients (Appendix Fig A3, online only). Responses at this dose lasted for at least a median of 9.0 months (range, 5.8 to ≥ 13.6 months; Table 4), with 2 patients still receiving treatment as of April 8, 2019. Overall, 6 patients had MRD-negative CRs (1 at 200 μg/d, 5 at 400 μg/d), with an additional 3 CRs (at 6.5, 100, and 800 μg/d), 2 VGPRs (at 400 and 800 μg/d), and 2 PRs (at 50 and 400 μg/d). Thus, the study ORR was 31% (95% CI, 17.6% to 47.1%; n = 13 of 42; see Appendix Table A2, online only, for the number of patients at each dose). Responders had a median of 6 prior lines of therapy as assessed at study entry per investigator; a post hoc analysis per Rajkumar et al[26] 2015 guidelines showed a median of 4 prior lines. The median time to any response was 1 month, with 11 of 13 patients (ie, all responders who were receiving ≥ 100 μg/d) responding in the first cycle (Fig 1C). Best responses occurred during cycle 1 (n = 4), cycle 2 (n = 2), cycle 3 (n = 5), or follow-up (n = 2). Responses lasted for at least a median of 8.4 months (range, 2.5 to ≥ 15.5 months) and were > 1 year in 3 patients; responses were ongoing at last observation for 7 (54%) of 13 patients. For the 3 patients with post-treatment data, their ongoing responses lasted for up to 11 months after treatment. One patient who discontinued treatment after 2 weeks because of polyneuropathy had a CR 8 months later without any subsequent therapy. MRD-negative responses lasted for a median of 9.6 months (range, 2.8 to ≥ 12.8 months). Responses were seen in patients in all cytogenetic risk categories; 5 of 13 responders had high-risk cytogenetics (Table 4).

***Biomarkers.*** Examination of baseline cell surface BCMA expression found that BCMA was expressed on myeloma cells in all patients, with no difference in expression levels by response status. There also was no difference between responders and nonresponders for percentage of plasma cells in the bone marrow that were BCMA positive or for the percentage of myeloma cells in the bone marrow at baseline (Appendix Figs A4A and A4B, online only). With regard to cell surface BCMA expression after relapse (none of the relapses were extramedullary), plasma cell infiltration was too low in the few patients with available data who experienced relapse while receiving AMG 420 (n = 3) to draw conclusions. There also was no difference in baseline programmed death ligand 1–positive myeloma cells by response status (Appendix Fig A4C). Responders displayed a rapid and sustained fall in soluble BCMA (sBCMA); sBCMA changes in the first weeks of treatment may provide an early indication of response (Fig 1D). Baseline sBCMA

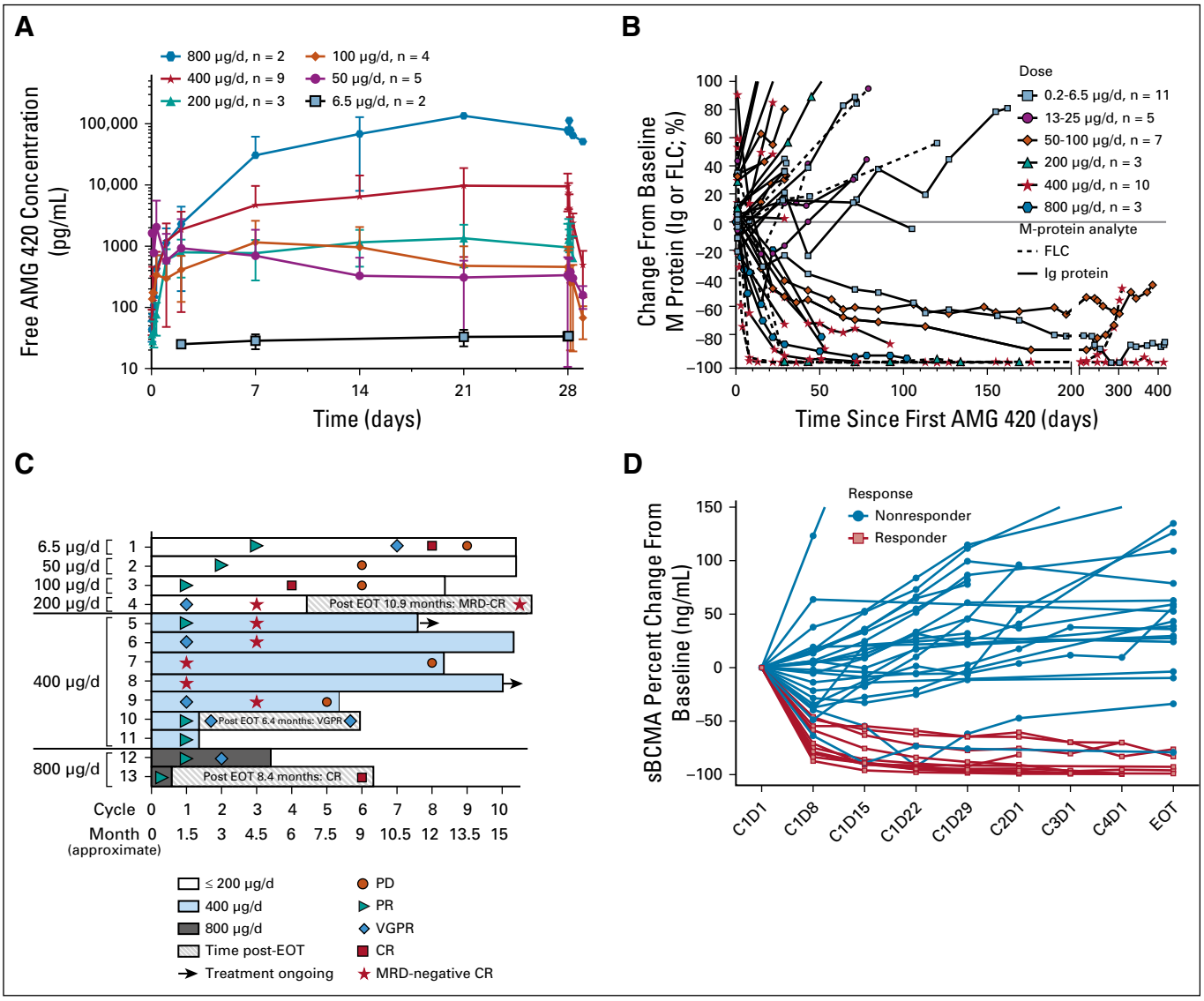


**FIG 1.** (A) Pharmacokinetics in cohorts with responding patients. Mean (standard deviation) free AMG 420 concentrations over time are shown in the plot for patients in dose cohorts at which responses were seen. (B) Kinetics of tumor response with AMG 420. Percent change from baseline for M protein (either immunoglobulin [Ig] or free light chain [FLC]) is shown over time on study for patients at different doses. Patients who did not have baseline values or postbaseline values sufficient to graph (ie, if values were only available for the first few days) were not included (n = 3). (C) Responding patients. In this diagram, details of individual responding patients show time of receipt of specific doses of AMG 420 and time in post-treatment follow-up. The various symbols indicate clinical response. Unless progressive disease (PD) was the last response indicated, patients were responding at last evaluation. (D) Change in soluble B-cell maturation antigen (sBCMA) over time. This plot shows the percent change from baseline sBCMA by response status (12 responders because 1 patient did not have a baseline sBCMA measurement; 26 nonresponders because 3 patients did not have a postbaseline response assessment). Cycles lasted 6 weeks, 4 weeks while on continuous intravenous infusion, and 2 weeks off treatment, with visits typically occurring around the indicated days (visit 1, day 1; visit 2, day 8; visit 3, day 15; visit 4, day 22; visit 5, days 29-30). C1D1, cycle 1, day 1 (etc); CR, complete response; EOT, end of treatment; MRD, minimal residual disease; PR, partial response; VGPR, very good partial response.



levels were 29 to 3,610 ng/mL; the limited number of patients in the study precluded the formation of any statistical conclusions with regard to baseline sBCMA concentrations in subgroups.

## DISCUSSION

In this first-in-human dose escalation study, AMG 420, a short half-life BiTE molecule that targets BCMA, demonstrated a high degree of clinical activity in patients with heavily pretreated multiple myeloma, irrespective of cytogenetic risk. There were no major toxicities before DLTs at 800 µg/d of CRS and polyneuropathy; a patient in the subsequent 400 µg/d dose expansion cohort also had a DLT of polyneuropathy. All 3 DLTs were fully reversible. Of doses tested in this study, 400 µg/d was the MTD. Overall, there was encouraging evidence of activity, with 13 of 42

**TABLE 3.** Cytokine Release Syndrome and Serious AEs

| Variable | No. (%) | No. of Patients With AEs at Each Grade | | | | |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 |
| No. of patients | 42 | | | | | |
| Infections serious AEs | | | | | | |
| All | 14 (33) | — | 4 | 8 | — | 2[b] |
| Pulmonary[a] | 6 (14) | — | 3 | 3 | — | — |
| Central line/port infections | 5 (12) | — | — | 5 | — | — |
| Adenovirus[b,c] | 1 (2) | — | — | — | — | 1 |
| Aspergillosis/influenza[b] | 1 (2) | — | — | — | — | 1 |
| Infection of unknown origin (fever)[d] | 1 (2) | — | 1 | — | — | — |
| Treatment-related serious AEs | | | | | | |
| Peripheral polyneuropathy | 2 (5) | — | — | 2 | — | — |
| Edema | 1 (2) | — | — | 1 | — | — |
| Cytokine release syndrome | | | | | | |
| All treatment related, maximum grade | 16 (38) | 13 | 2 | 1 | — | — |

Abbreviation: AE, adverse event.

[a]Includes pneumonia (n = 4) and 1 each of bronchiopulmonary infection and infectious pneumopathy.

[b]One patient died as a result of aspergillosis/influenza and 1 as a result of fulminant hepatitis related to adenovirus infection; neither death was treatment related.

[c]Death in 400 μg/d cohort as a result of fulminant hepatitis related to adenovirus infection in the setting of immunosuppression not considered related to AMG 420. The trial sponsor held enrollment of new patients while responding to regulatory questions; subsequently, it was decided to halt enrollment after 10 patients had enrolled at 400 μg/d because an additional study of AMG 420 was being initiated.

[d]Accompanied by treatment-related SAE of grade 1 fever.

patients during dose escalation responding with a median response time of 1 month. At 400 μg/d, 7 (70%) of 10 patients had responses, all of which started in the first cycle, with a best response of MRD-negative CR in 5 patients (50%). Four patients attained CRs at other doses, including 1 MRD-negative CR. While these responses lasted for a median of 8 months as of this data cutoff, because this was a phase I study with incomplete follow-up, the true duration of response may be under-reported. Biomarker data from this initial data set indicate that responses are not related to baseline cell surface BCMA expression or the percentage of BCMA-positive plasma cells or tumor burden. Limitations of this study include exclusion of patients with extramedullary disease; exclusion of those with prior allogeneic transplant (as also seen in trials of other anti-BCMA agents); absence of subgroup analyses because of the limited number of patients; and an MRD definition of $< 1$ tumor cell/$10^4$ bone marrow cells, which is less stringent than current standards but comparable to those of other trials published recently.[8,9]

Response rates and safety profiles with therapies targeting BCMA in relapsed/refractory multiple myeloma have varied. For the antibody-drug conjugate GSK2857916, the response rate was 60% (n = 21 of 35), with a median time to response of 1.4 months and a median response duration of 14.3 months.[18,27] Corneal events were reported in 24 of 35 patients and frequently led to dose reductions (46%) and dose delays/interruptions (49%). Reported response rates for patients who were successfully able to receive anti-BCMA CAR-T-cell therapies have been 48%-88% (48%, 83%, 85%, 88%, and 88%),[7-11] with MRD-negative rates of 16%-69% (16%, 48%, 66%, and 69%), although there were differences between number treated and intended to treat (24 *v* 27,[7] 33 *v* 36,[9] and 25 *v* 29[10]). Where reported, median response onset was 2-4 weeks, and median response duration was 4-14 months. Of note, 1 patient with a best response of VGPR had loss of BCMA expression 56 weeks after CAR-T-cell infusion.[7] Rates of grade ≥ 3 CRS with CAR-T cells were 6%-41% (6%, 7%, 32%, 38%, and 41%; grades per Lee et al,[28] Porter et al,[29] or Neelapu et al[30]), with tocilizumab use rates of 21%-53% and vasopressor support use rates of 11%-38%. Of note, in the CAR-BCMA study, after severe CRS of grades 4 and 3, respectively, in the first 2 patients who received the highest CAR-T-cell dose, both of whom had baseline bone marrow plasma cells ≥ 80%, subsequent patients were required to have < 30% bone marrow plasma cell percentages. Grade 3/4 CRS was seen in 4 of the subsequent 14 patients.[7] Neurotoxicity with CAR-T cells was variable in presentation and was seen in 2%-42% of patients.[7-10] As in our study, serious infections were seen with CAR-T-cell treatment (eg, respiratory, fungemia, sepsis).[7,9-11]

Results with AMG 420 show comparable response rates and onset and duration of responses as seen with CAR-T cells. The rate of CTCAE grade ≥ 3 CRS was 2% (n = 1 of 42), lower than reported with CAR-T cells; only 1 patient was treated with tocilizumab. Neurotoxicity with AMG 420 was not common, with 1 grade 3 asthenia and 2 grade 3 peripheral polyneuropathies, all of which resolved. The types and relatively low rates of neurotoxicity and absence of CNS toxicity seen here, compared with the BiTE molecule blinatumomab,[19] may reflect the difference in target (CD19) and/or disease (acute lymphoblastic leukemia). The incidence of serious infections in this study (n = 14; 33%) indicates a need to develop comprehensive prophylaxis protocols. Careful evaluation of this in future trials will enable development of optimal management guidelines.

In conclusion, results reported here indicate that additional clinical investigation is warranted. Besides this first-in-human trial, patients are enrolling in a phase Ib trial. While the data described here provide important proof-of-concept evidence for BCMA-directed BiTE molecules as a compelling therapeutic strategy in multiple myeloma, continuous intravenous infusion presents logistical challenges for patients and health care systems. Moving forward, the sponsor solely decided to focus further development of the BCMA BiTE molecules on the half-life–extended BCMA

**TABLE 4.** Responding Patients

| Age (years) | No. Prior Lines at Study Entry: Per Investigator | No. Prior Lines at Study Entry: Post Hoc Per Rajkumar 2015 Guidelines[26] | No. SCT | Baseline BM PC, %[a] | Cytogenetic Risk[25] (IMWG 2016[24] if Different)/Findings | Dose, μg/d × No. of Cycles | No. of Months Treated | Discontinuation Reason | Duration of Response (follow-up), Months | Best Response (cycle) |
|---|---|---|---|---|---|---|---|---|---|---|
| 66 | 4 | 1 | 2 | 10 | Standard/t(11;14) | 6.5 × 10 | 13.7 | NA (10 cycles) | 8.1 (9.9) | CR (8) |
| 59 | 6 | 2 | 2 | 2 | Standard/none | 50 × 10 | 13.6 | NA (10 cycles) | 5.3 (21.7) | PR (2-5) |
| 66 | 6 | 3 | 1 | 2 | Standard/none | 100 × 8 | 11.3 | PD | 6.2 (9.5) | CR (4-5) |
| 77 | 7 | 6[b] | 0 | 6 | High/del(1p), +1q, del(17p) | 200 × 4 | 5.3 | Port infection | 15.5 (15.5) | MRD− CR (3-4 to 10.9 months post-EOT) |
| 39 | 4 | 2 | 2 | 8 | Intermediate (standard)/del(13q), del(16q) | 400 × 7 | 9.7 | NA (ongoing)[c] | 8.8 (8.8) | MRD− CR (3-7) |
| 54 | 5 | 4 | 2 | 25 | Standard/del(14q), del(16q) | 400 × 10 | 15.5 | NA (10 cycles) | 13.4 (13.4) | MRD− CR (3-10) |
| 55 | 8 | 5 | 2 | 60 | Intermediate (standard)/del(13q) | 400 × 8 | 9.5 | PD | 9.1 (9.1) | MRD− CR (1-7) |
| 70 | 3 | 1 | 2 | 80 | High/t(11;14), del(8p), del(13q), del(16q), del(17p) | 400 × 10 | 12.9 | NA (completing cycle 10)[c] | 13.6 (13.6) | MRD− CR (1-10) |
| 69 | 5 | 5[b] | 1 | 5 | High/5(11;14), del(1p), monosomy 13, +1q, del(8p), del(17p) | 400 × 0.7, 200 × 3.8, 400 × 0.5 | 5.1 | PD | 5.8 (5.8) | MRD− CR (3-4) |
| 54 | 6 | 3[b] | 2 | 80 | Standard/trisomy 9q34 | 400 × 1 | 1.0 | PN | 7.2 (7.2) | VGPR (EOT to 6.4 months post-EOT) |
| 73 | 5 | 5[b] | 0 | 12 | Standard/none | 400 × 1 | 1.0 | Death | NA[d] | PR (1)[d] |
| 79 | 6 | 5 | 3 | 28 | Intermediate (high)/t(4;14), del(1p), +1q, del(13q) | 800 × 2, 400 × 1 | 3.3 | Withdrew consent | 2.5 (2.5) | VGPR (2-3) |
| 62 | 6 | 5[b] | 2 | 90 | Standard(high)/+1q | 800 × 0.5 | 0.5 | PN | 8.6 (8.6) | PR (1), CR (8.4 months post-EOT) |

NOTE. At baseline unless otherwise indicated. All responders were white. Overall for the study, daratumumab treatment was reported for 12 (29%) of 42 patients, with 6 of 10 of those at 400 μg/d having prior daratumumab treatment and 2 of 3 of those at 800 μg/d having prior daratumumab treatment.

Abbreviations: BM, bone marrow; CR, complete response; del, deletion; EOT, end of treatment; IMWG, International Myeloma Working Group; MRD−, minimal residual disease negative; NA, not applicable; PC, plasma cell; PD, progressive disease; PN, polyneuropathy; PR, partial response; SCT, stem-cell transplant; VGPR, very good partial response.

[a]By morphology.

[b]Including daratumumab.

[c]Still on study; months of treatment as of last reported dose.

[d]Patient died 1 day after PR; hence, no duration.

BiTE molecule (AMG 701) and intermittent dosing of AMG 420, both of which are being studied in ongoing phase I trials. Specifically, the safety, efficacy, and pharmacokinetics of subcutaneously administered AMG 420 that targets the equivalent free AMG 420 exposures achieved in patients who respond to continuous intravenous dosing (Appendix Fig A3) will be evaluated. These studies will provide additional data on BiTE molecules targeted against BCMA as potential off-the-shelf therapies for patients with relapsed/refractory multiple myeloma.


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**Conception and design:** All authors
**Provision of study material or patients:** All authors
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**Manuscript writing:** All authors
**Final approval of manuscript:** All authors
**Accountable for all aspects of the work:** All authors

## DATA AVAILABILITY STATEMENT

Qualified researchers may request data from this study. Complete details are available at https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices


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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Anti–B-Cell Maturation Antigen BiTE Molecule AMG 420 Induces Responses in Multiple Myeloma**

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## APPENDIX

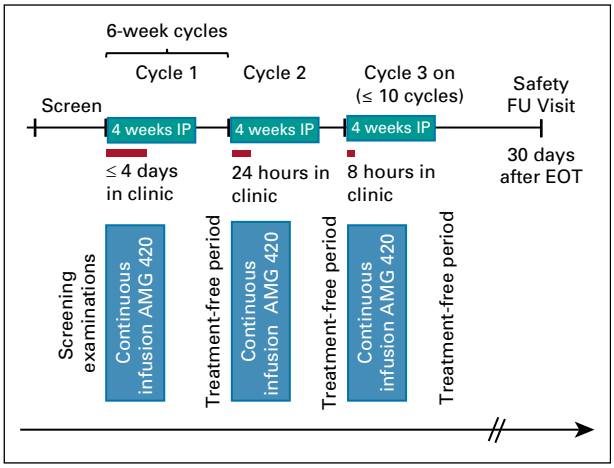


**FIG A1.** Study design. A general schematic of the study is shown, with time on and off treatment. Patients were to be treated for up to 5 cycles or until disease progression/further anticancer treatment, toxicity, withdrawal of consent, or investigator decision. Five more cycles could be given for benefit per investigator for a total of ≤ 10 cycles. EOT, end of treatment; FU, follow-up; IP, investigational product.

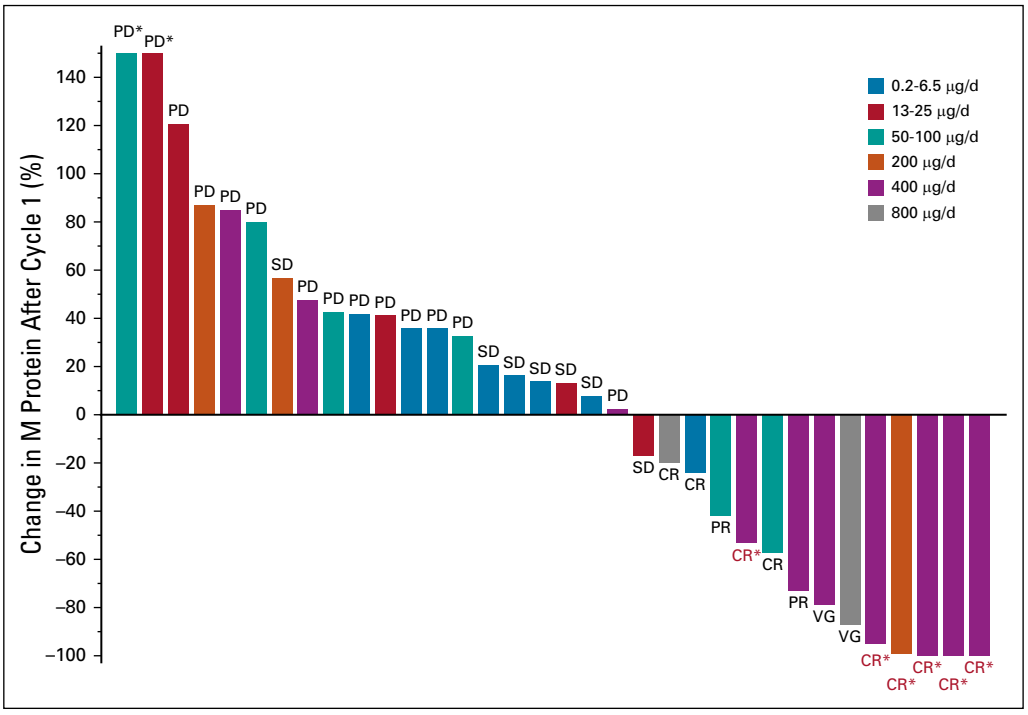


**FIG A2.** Cycle 1 change in M protein with best overall response. Best overall responses per investigator are shown next to percent change in M protein in the first cycle. Patients who lacked baseline M-protein values (n = 2), M-protein values at least 2 weeks postbaseline (n = 3), or postbaseline response assessments (n = 3 of whom 2 were treated ≤ 14 days before discontinuation because of an adverse event) were not included in this graph. CR, complete response; CR*, minimal residual disease–negative CR; PD, progressive disease; PD*, progressive disease with increase in M protein > 150%; PR, partial response; SD, stable disease; VG, very good partial response.

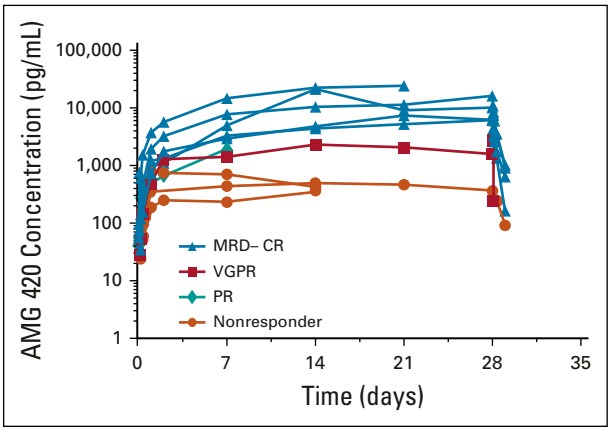


**FIG A3.** Free AMG 420 pharmacokinetic profiles. Shown are individual patient free AMG 420 concentrations *v* time over the first 28 days of the first treatment cycle during continuous intravenous infusion of 400 μg/d; also indicated is best response while on study. MRD− CR, minimal residual disease–negative complete response; PR, partial response; VGPR, very good partial response.

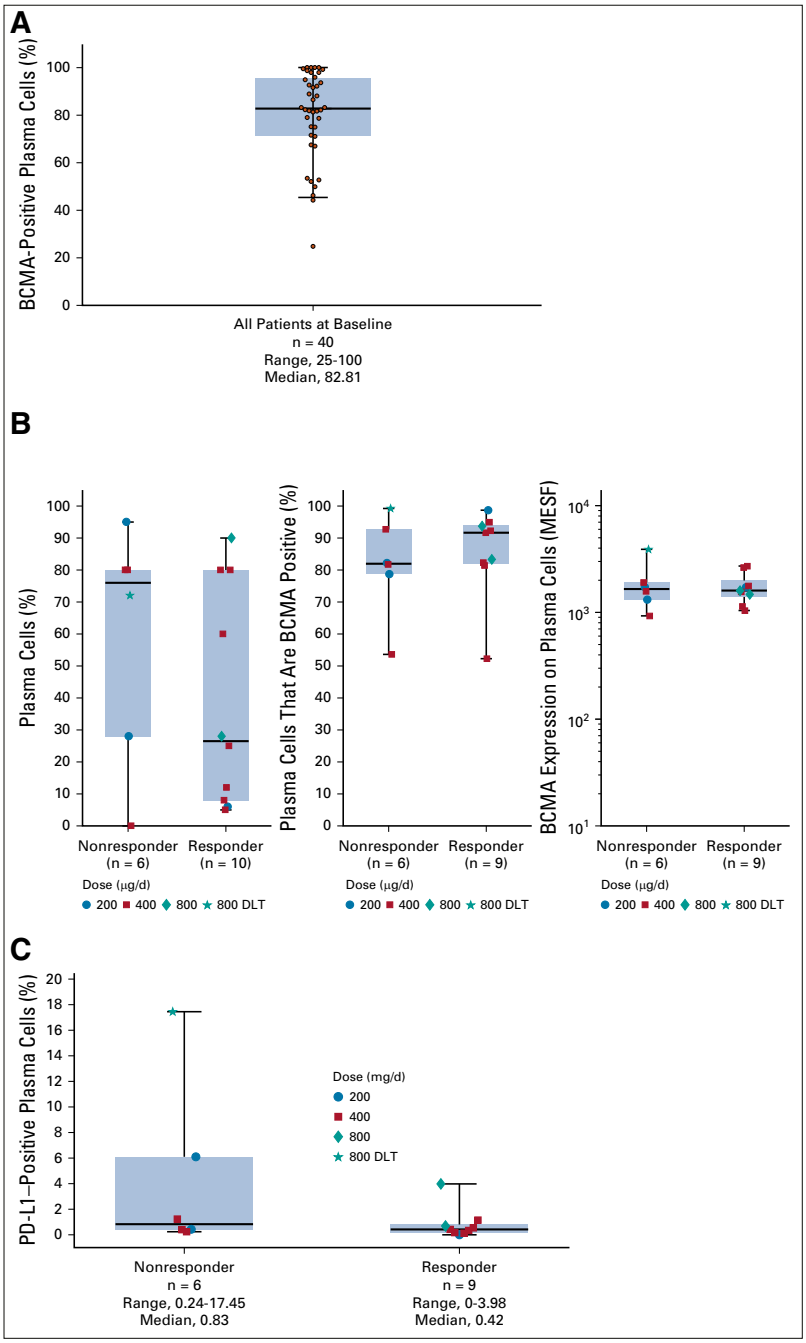


**FIG A4.** Baseline B-cell maturation antigen (BCMA) expression. Responder analyses were performed with patients who received ≥ 200 μg/d (n = 16) because patients at lower doses had not received sufficient drug to make a response analysis meaningful. (A) BCMA expressed on myeloma plasma cells. Plot shows the percentage of $CD138^{+}CD38^{+}$ plasma cells that were BCMA positive by flow cytometry. Data are shown for all patients in the study who had bone marrow flow cytometry data from the screening bone marrow aspirate. (B) Baseline BCMA expression on plasma cells by response. The left panel shows percent plasma cells in bone marrow aspirate as determined by morphology. The middle panel shows the percentage of $CD138^{+}CD38^{+}$ plasma cells that were BCMA positive by flow cytometry on bone marrow aspirates. The right panel shows normalized BCMA expression on BCMA-positive plasma cells in bone marrow aspirates by flow cytometry. (C) Percentage of programmed cell ligand 1 (PD-L1)–positive plasma cells by response. Shown are the percentages of plasma cells in the bone marrow that were PD-L1 positive at the time of screening by response status. DLT, dose-limiting toxicity; MESF, molecules of equivalent soluble fluorochrome.

**TABLE A1.** Patients With Peripheral PN

| Neuropathy Evaluation/ Treatment | Patient in 800 μg/d Cohort | | Patient in Subsequent 400 μg/d Dose Expansion Cohort[a] | |
|---|---|---|---|---|
| | At Presentation | Follow-Up | At Presentation | Follow-Up |
| Symptoms | Grade 3 PN of legs | Returned to baseline | Grade 3 PN of arms and legs, including paresthesia, and double vision | Returned to baseline sensory grade 1 PN |
| Physical examination | Sensorimotor disorder with ataxia of legs and arms, more so on right side than left side | Returned to baseline | Paresis of lower limbs (grade 4/5), sensory paresthesia from feet to abdomen and in lower arms | Returned to baseline sensory grade 1 PN |
| Autoimmune laboratory | Negative for antineural antigen IgG immunofluorescence | — | — | — |
| Neurology consult impression | Autoimmune-mediated subacute sensorimotor PN | Marked improvement | Suspected chronic inflammatory demyelinating PN | — |
| Cranial CT | — | — | Osteolyses, no bleeding, no other pathologic findings | — |
| Cranial MRI | No pathologic findings in cranial MRI, spinal cord, nerves | — | Enhanced contrast medium uptake in basal cranial nerve and cervical spinal nerve may indicate neuritis, polyradiculitis, or meningeosis | Only minimal enhanced contrast uptake in basal cranial nerve and cervical spinal nerve |
| Lumbar puncture | Elevated protein, 90.3 mg/dL (normal, < 50 mg/dL); normal glucose; no pleocytosis<br>No viral infections[b]<br>No bacterial infection<br>Flow: no plasma cells, few T cells | — | Elevated protein, 192.9 mg/dL (normal, < 50 mg/dL); normal glucose, lactate, LDH, cell count; no suspicious cells | — |
| Biopsy | — | — | — | — |
| Nerve conduction velocity | Axonal and demyelinating sensorimotor nerve damage pattern | Marked improvement of axonal and demyelinating sensorimotor nerve damage pattern | In motor nerve velocity, clear latency delay and reduction of nerve conduction, reduced amplitude | — |
| Treatment of neuropathy | 5 days of IVIg (0.4 g/kg) | — | 5 days of IVIg (0.4 g/kg) and 3 days of prednisolone (100 mg); improvement started day 7 | — |

Abbreviations: CT, computed tomography; Ig, immunoglobulin; IVIg, intravenous immunoglobulin; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PN, polyneuropathy.

[a]This patient had a history of chronic inflammatory demyelinating PN with lenalidomide 3 years prior, and in 2001, 13 years before the diagnosis of multiple myeloma, this patient had Guillain-Barré syndrome that responded to immunosuppressive therapy of corticosteroids, azathioprine, and Igs.

[b]Tested for herpes virus 1 and 2, varicella, Epstein-Barr virus, cytomegalovirus, human herpes virus 6, John Cunningham virus, and adenovirus.

**TABLE A2.** Patients in Each Dose Cohort

| Dose Cohort (μg/d) | No. of Patients (N = 42) |
|---|---|
| 0.2 | 1 |
| 0.4 | 1 |
| 0.8 | 2 |
| 1.6 | 1 |
| 3.2 | 3 |
| 6.5 | 3 |
| 13 | 3 |
| 25 | 3 |
| 50 | 5 |
| 100 | 4 |
| 200 | 3 |
| 400 | 10 |
| 800 | 3 |