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# A Phase I Dose-Escalation Study of Antibody BI-505 in Relapsed/Refractory Multiple Myeloma

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## Abstract

**Purpose:** This multicenter, first-in-human study evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of BI-505, a human anti-ICAM-1 monoclonal antibody, in advanced relapsed/refractory multiple myeloma patients.

**Experimental Design:** BI-505 was given intravenously, every 2 weeks, at escalating doses from 0.0004 to 20 mg/kg, with extension of therapy until disease progression for responding or stable patients receiving 0.09 mg/kg or higher doses.

**Results:** A total of 35 patients were enrolled. The most common adverse events were fatigue, pyrexia, headache, and nausea. Adverse events were generally mild to moderate, and those attributed to study medication were mostly limited to the first dose and manageable with premedication and slower infusion. No maximum tolerated dose was identified. BI-505's half-life increased with dose while clearance decreased, suggesting target-mediated clearance. The ICAM-1 epitopes on patient bone marrow myeloma were completely saturated at 10 mg/kg doses. Using the International Myeloma Working Group criteria, 7 patients on extended therapy had stable disease for more than 2 months.

**Conclusions:** BI-505 can be safely administered at doses that saturate myeloma cell ICAM-1 receptors in patients. This study was registered at www.clinicaltrials.gov (NCT01025206).
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## Introduction

The introduction of new therapies, including immunomodulatory drugs (IMiD) and proteasome inhibitors, during the last decade has significantly improved survival and outcome in multiple myeloma. However, many multiple myeloma patients still relapse and event-free survival decreases progressively with each relapse. The outlook is very poor for relapsed and refractory patients, with median survival time of less than 1 year (1–4). Additional treatment modalities are therefore needed to improve survival for multiple myeloma patients.

BI-505 is a fully human high-affinity IgG1 antibody, which was isolated from a highly diverse human phage-antibody library based on its functional ability to induce programmed cell death of tumor cells (5). BI-505 binds to intercellular adhesion molecule-1 (ICAM-1), suggesting a previously unrecognized role for this receptor as a therapeutic target in cancer. The BI-505 epitope is strongly expressed on the surface of multiple myeloma cells from both newly diagnosed and relapsed patients (5). BI-505 has potent macrophage-dependent anti-myeloma activity. It has been shown to enhance survival in advanced disseminated murine models of myeloma compared with currently used treatments, and to inhibit primary myeloma cell growth and bone damage in an SCID-hu model when used in combination with lenalidomide and bortezomib (5).

This first-in-human study was conducted to determine the maximum tolerated dose (MTD) of BI-505 when given as a mono-therapy, and to characterize its safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with refractory/relapsed multiple myeloma.

## Materials and Methods

### Patient population

The study included adults with relapsed or refractory myeloma (after at least two different previous therapies), an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or lower, and life expectancy greater than 3 months. All patients had measurable levels of M component in serum (≥1.0 g/dL) or in urine (≥200 mg per 24 hours) or serum immunoglobulin free light chain (≥10 mg/dL) at inclusion in the study. All had

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**Note:** Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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## Translational Relevance

BI-505 is a fully human high-affinity IgG1 antibody, which was isolated from a highly diverse human phage-antibody library based on its functional ability to induce programmed cell death of tumor cells. BI-505 binds to intercellular adhesion molecule-1 (ICAM-1), suggesting a previously unrecognized role for this receptor as a therapeutic target in cancer. The BI-505 epitope is strongly expressed on the surface of multiple myeloma cells from both newly diagnosed and relapsed patients. BI-505 has potent macrophage-dependent antimyeloma activity. It has been shown to enhance survival in advanced disseminated murine models of myeloma compared with currently used treatments, and to inhibit primary myeloma cell growth and bone damage in an SCID-hu model when used in combination with lenalidomide and bortezomib. This first-in-human study was conducted to determine the maximum tolerated dose (MTD) of BI-505 when given as a monotherapy, and to characterize its safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with refractory/relapsed multiple myeloma.

adequate hepatic function (transaminases $\leq$ 2.5 times the upper limit of normal (ULN) and direct bilirubin $\leq$ 1.5 times ULN), adequate renal function (calculated creatinine clearance $\geq$ 50 mL/min), and adequate hematologic reserve (hemoglobin level > 8 g/dL in the previous 14 days, ANC > 1,000/mm$^3$ and platelets > 50,000/mm$^3$).

Patients were excluded if they had received any other antimyeloma treatment within 4 weeks before the first dose of the study drug, and they should have recovered from any toxic effects of earlier chemotherapy (grade $\leq$ 1 except for neuropathy, where remaining grade $\leq$ 2 was accepted). They were also excluded if they had received allogeneic bone marrow/stem cell transplantation within 12 months before the first dose, and if they had chronic graft-versus-host disease or any other prior malignancy in the previous 2 years, with the exceptions of multiple myeloma, adequately treated basal cell or squamous cell skin cancer, cervical carcinoma *in situ*, prostate cancer Gleason < 6 and prostate-specific antigen (PSA) < 10 ng/mL, radically excised lobular or ductal carcinoma *in situ* (LCIS/DCIS) $\leq$ 15 mm breast cancer in women over 40 years old, or any malignancy for which the subject had undergone potentially curative therapy with no evidence of the disease for 3 years.

Patients were also excluded if they had comorbidity such as cerebrovascular disease or atrial fibrillation (unless more than 2 years previously and well controlled with adequate medication); other severe conditions requiring treatment and close monitoring, such as cardiac failure of New York Heart Association class III or higher, unstable coronary disease, or oxygen-dependent chronic obstructive pulmonary disease (COPD); or other clinical findings indicating cardiac or renal amyloid light chain (AL) amyloidosis. Study patients were not allowed to have evidence of significant active infection, requiring intravenous antibiotics, within 14 days before inclusion; to have substance abuse or other concurrent medical conditions that, in the investigators' opinion, could confound study interpretation or affect the patient's ability to tolerate or complete the study; or to have had significant autoimmune disease requiring systemic treatment with steroids or other immunosuppressive drugs during the previous 2 years. The patients were not allowed to be HIV- or hepatitis B- or C-positive.

### Study design

This was a multicenter, open-label, dose-escalation phase I study designed to evaluate BI-505 administered by intravenous (i.v.) infusion in patients with relapsed/refractory multiple myeloma. Patients in the first five dose groups (with doses of 0.0004 mg/kg; 0.001 mg/kg; 0.003 mg/kg; 0.009 mg/kg; 0.03 mg/kg) were only given two i.v. infusions of BI-505 on day 1, and on day 15 (one cycle) and were thereafter finished with the study treatment. Patients in dose groups 6 to 11 (with doses of 0.09 mg/kg; 0.30 mg/kg; 0.90 mg/kg; 3.00 mg/kg; 10.00 mg/kg; 20.00 mg/kg) had the option to continue treatment with BI-505 (administered every 2 weeks) pending disease progression, unacceptable toxicity, withdrawal of consent, or the investigators' decision to end treatment. An end-of-study evaluation was performed 28 days after the last BI-505 dose was administered.

Dose groups 1 to 5 consisted of 1 patient per group and the subsequent dose groups consisted of 3 patients per group. However, if a drug-related toxicity of grade 2 or higher was seen in one of the first five cohorts, 2 additional patients were to be enrolled in that cohort. If a dose-limiting toxicity (DLT) was observed in any dose group, that cohort was reinforced to a total of 6 patients (as happened in one cohort). If a second patient in a dose group had a DLT, inclusion in that cohort was to be stopped and the dose level below was identified as MTD. A data safety monitoring committee reviewed the safety data for each cohort before the start of the next dose group. A one-week observation period was included between administration of the first dose and the start of the second patient in all cohorts with more than 1 patient.

BI-505 was administrated i.v. over approximately 2 hours and premedication was not required for dose groups 1 to 7. Following the observation of infusion-related reactions in dose group 8 (0.9 mg/kg), all patients received an antihistamine and acetaminophen/paracetamol before each BI-505 infusion. In addition, corticosteroids (prednisolon 25–50 mg or hydrocortisone 50–100 mg) were administered before the first dose in the 10- and 20-mg/kg cohorts. The first dose of BI-505 was infused over 4 hours in the 10 mg/kg cohort and 5 hours in the 20 mg/kg cohort.

This study was approved by the institutional review boards of the participating centers, overseen by a data safety monitoring committee, and conducted according to the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. It was registered at www.clinicaltrials.gov (identifier NCT01025206). Written informed consent was obtained from all patients before enrollment.

### Safety and efficacy assessments

Adverse events (AE) were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v3.0). A DLT was defined as any grade 3 or greater nonhematologic toxicity or any grade 4 hematologic toxicity, provided the toxicity was possibly related to treatment with BI-505. Other safety evaluations used were physical examinations including Eastern Cooperative Oncology Group (ECOG) performance status assessment, vital signs, laboratory tests (including complete blood count, clinical chemistry, coagulation, and urine analysis), electrocardiograms (ECG), and BI-505 immunogenicity testing.



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As a secondary objective, treatment responses were determined using the International Myeloma Working Group (IMWG) criteria, which included measurements of serum and urine M-protein, serum free light chains, and plasma cell levels in bone marrow.

### Pharmacokinetics

Blood samples for analysis of BI-505 concentration were collected from all dose groups starting with group 6. Eight pharmacokinetics samples were taken to characterize the initial dose and in connection with each consecutive dose, samples were collected close to trough and $C_{max}$. Serum concentrations were determined by an ELISA-based immunoassay (assay range 100–8,000 ng/mL). The PK after first dose and multiple dosing intervals were evaluated using noncompartmental and two-compartmental analysis, respectively (WinNonlin Version 5.2, Pharsight Corporation). Geometric mean values were used for all parameters except $t_{1/2}$ and $t_{max}$, where harmonic mean and median were used, respectively.

### Immunogenicity

Immunogenicity samples for detection of anti-BI-505 antibodies were collected predose on day 22 and at the end of the study. Samples were also collected predose on day 57 for patients on continued treatment. A qualitative and semi quantitative electrochemiluminescent immunoassay (Meso Scale Discovery platform) was used to detect the presence of BI-505 antibodies in serum samples. The assay was divided into three steps as follows. All samples were initially screened and positive samples were subjected to a confirmatory assay, where samples were preincubated with buffer, or buffer containing BI-505, before analysis. Samples with a true positive antibody response showed inhibition (mean 53.6%) in the response for the sample with buffer containing BI-505 as compared with the sample with buffer alone. These confirmed positive samples underwent a titer analysis, to allow semi-quantification. Affinity-purified goat-anti-BI-505 polyclonal antibodies were used for the positive control samples.

### Pharmacodynamics

The pharmacodynamic profile of BI-505 was measured for dosing groups 6 to 11 by assessment of the saturation of ICAM-1 on plasma cells in bone marrow aspirates/biopsies at screening and 48 hours after the end of first infusion. In some cases a sample was taken before dosing on day 15 or before a subsequent dosing to assess saturation of ICAM-1 at trough level. The levels of BI-505-bound and free ICAM-1 cell-surface receptors on multiple myeloma in bone marrow samples were assessed using two labeled noncompeting ICAM-1 antibodies; BI-505 and enlimomab (a human ICAM-1-specific monoclonal murine antibody that recognize a different epitope compared with BI-505 and does not compete with binding to ICAM-1). In the assay, enlimomab was used to determine the expression of ICAM-1 on the patients' multiple myeloma cells during the treatment. To identify multiple myeloma cells, the samples were also labeled with monoclonal antibodies for CD38, CD138, and CD19 and analyzed by flow cytometry. The screening sample was used to generate a binding curve and to identify the concentration at which all ICAM-1 epitopes on the multiple myeloma cells were bound with labeled BI-505 (i.e., the concentration at which saturation occurred). This concentration was found to be around 1 μg/mL, with some patient variation. A blocking curve was also generated from the screening sample using unlabeled BI-505 titrated from 0 to 1,000 μg/mL and labeled BI-505 at a fixed concentration of 10 μg/mL. The blocking curve was used to calculate BI-505 receptor occupancy on multiple myeloma cells from the 48-hour postdose sample after the first infusion and/or subsequent pre-dose samples.

### Statistical analysis

The primary endpoint for this study was safety, therefore no formal hypothesis testing was planned or conducted. For continuous data, summary statistics included the arithmetic mean and standard deviation (SD). The geometric mean and coefficient of variation (CV) are presented for all PK parameters except time of the maximum observed serum concentration ($t_{max}$), percentage of area under the serum concentration-time curve (AUC) extrapolated from the time of last quantifiable serum concentration ($t_{last}$) to infinity (%$AUC_{extrap}$). The harmonic mean is also presented for the apparent serum-terminal elimination half-life ($t_{1/2}$). For categorical data, frequency count and percentages are presented. Data analyses were performed using SAS Version 8.2 (SAS Institute Inc.).

## Results

The study was conducted between December 2009 and February 2013 at two sites in the United States, two sites in Sweden, two sites in Belgium, and one site in Denmark. Study disposition is detailed in Table 1. A total of 38 patients were screened, of whom 35 were enrolled into the 11 dosing cohorts: 1 in the 0.0004-mg/kg cohort, 1 in the 0.001-mg/kg cohort, 1 in the 0.003-mg/kg cohort, 1 in the 0.009-mg/kg cohort, 1 in the 0.03-mg/kg cohort, 3 in the 0.09-mg/kg cohort, 3 in the 0.3-mg/kg cohort, 3 in the 0.9-mg/kg cohort, 7 in the 3.0-mg/kg cohort, 10 in the 10.0-mg/kg cohort, and 4 in the 20.0-mg/kg cohort. Thirty-four patients received study treatment, ranging from 1 to 13 infusions. One patient in the 20.0-mg/kg cohort was withdrawn before receiving study treatment. Five patients discontinued treatment after the first dose due to treatment-related AEs. Twenty-nine patients completed cycle 1. Of the 29 patients who completed cycle 1, 12 discontinued before starting cycle 2 due to protocol stipulations (5 patients, in dose group 1–5), voluntary withdrawal (1 patient), treatment-related AEs (1 patient), or disease

**Table 1.** Patient disposition

| Patient disposition | *n* |
|---|---|
| Screened | 38 |
| Screen failure | 3 |
| Enrolled | 35 |
| Discontinued before first dose | 1 |
| Dosed patients | 34 |
| Discontinued before second dose | 5 |
| Completed cycle 1 | 29 |
| Discontinuation before cycle 2 | 12 |
| Not eligible for continued treatment | 5 |
| Voluntary withdrawal | 1 |
| Treatment-emergent AE | 1 |
| Disease progression | 5 |
| Received extended treatment | 17 |
| Voluntary withdrawal | 4 |
| Treatment-emergent AE | 2 |
| Disease progression | 11 |
| Deaths | 3[a] |

[a]Two patients died due to progressive disease, and 1 patient died due to an infection, unrelated to BI-505.



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**Table 2.** Patient demographics and baseline characteristics

| Characteristics | Value (range) |
|---|---|
| Patients, *n* | 34 |
| Median age, y (range) | 62 (46–79) |
| Body weight, kg (range) | 78 (54–128) |
| Sex, *n* (%) | |
| Male | 24 (71%) |
| Female | 10 (29%) |
| Race, *n* (%) | |
| White | 30 (88%) |
| Black or African heritage | 2 (6%) |
| Asian | 1 (3%) |
| Other | 1 (3%) |
| Performance status; ECOG, *n* (%) | |
| 0 | 19 (56%) |
| 1 | 14 (41%) |
| 2 | 1 (3%) |
| Median time since diagnosis, y (range) | 5.7 (1.6–19) |
| M-component, *n* (%) | |
| IgG | 25 (74%) |
| IgA | 6 (18%) |
| IgD | 1 (3%) |
| Free light chain disease (kappa) | 2 (6%) |
| Prior multiple myeloma treatments | |
| Median no., *n* (range) | 6 (2–12) |
| Autologous stem cell transplant, *n* (%) | 29 (85%) |
| Any IMiDs in earlier treatments, *n* (%) | 27 (79%) |
| Lenalidomide, *n* (%) | 21 (62%) |
| Thalidomide, *n* (%) | 23 (68%) |
| Bortezomib in earlier treatments, *n* (%) | 29 (85%) |

progression (5 patients). The 17 patients who received continued/extended treatment eventually discontinued due to voluntary withdrawal (4 patients), treatment-related AEs (2 patients) or disease progression (11 patients). Three patients died during the study.

Patient demographics and disease characteristics are presented in Table 2. Most patients were Caucasian, with a median age of 62 years and heavily pretreated with a median of 6 prior lines of myeloma treatment. Most patients had received prior autotransplants (85%), IMiD therapy (79%; lenalidomide in 62% and thalidomide in 68%), and the proteasome inhibitor bortezomib (85%).

### Safety

Only one DLT was reported in this study: a patient in the 3-mg/kg dose group who was hospitalized after the first infusion due to a grade 3 headache that resolved spontaneously after 48 hours. The patient chose to discontinue the study. As only one DLT was reported, the MTD was not reached in this trial with doses up to 20 mg/kg.

### Adverse events

Overall, 33 out of 34 patients (97%) reported AEs. The total of 358 AEs reported were divided into the following severity grade: grade 1, $n = 192$ (54%); grade 2, $n = 130$ (36%); grade 3, $n = 29$ (8%); grade 4, $n = 7$ (2%); grade 5, $n = 0$ (0%). The most frequent AEs were fatigue (47%), pyrexia (32%), headache (32%), nausea (29%), and chills (24%). AEs related to BI-505 treatment were reported in 26 patients (76%), and are summarized in Table 3. Most of these AEs (95.9%) were graded 1 or 2 in severity. Only six AEs with severity grade 3 and a possibly or likely relationship to BI-505 were reported (headache, neutropenia, lymphopenia, thrombocytopenia). No grade 4 or 5 AEs with a possibly or likely relationship to BI-505 were reported. Infusion-related reactions and laboratory abnormalities were common during or after the first infusion and included pyrexia, headache, chills, and elevated C-reactive protein (CRP). In addition, some patients experienced fatigue (26%) and nausea (21%). Once these cytokine-related AEs became more frequent, a premedication regimen consisting of corticosteroids, antihistamine, and acetaminophen/paracetamol was administered before first infusion of BI-505 as well as before subsequent infusions if needed. At doses of $\geq$10 mg/kg, BI-505 was administered at a reduced rate (30 mL/h) during the first 30 minutes of infusion, followed by a gradually increased infusion rate, with the aim to complete the infusion (250 mL in total) within 2 hours. The infusion-times were 2 to 5 hours for 10 and 20 mg/kg doses.

A total of 26 serious AEs (grades 3–5) were reported in 14 patients (41%). Three of these serious AEs were fatal. Two patients died of disease progression (3 and 10 mg/kg doses) and 1 patient died of sepsis (following 10 mg/kg doses). The patient with sepsis had progressive disease after two doses of BI-505 and stopped BI-505 treatment. The patient developed neutropenia after salvage chemotherapy and was then hospitalized with sepsis 48 days after the last BI-505 infusion. These fatal serious AEs were therefore considered unrelated to BI-505 administration. Twelve serious AEs (in 10 patients) occurred within 2 days of the BI-505 infusion. Ten of the 12 were considered to be likely or possibly related to BI-505 headache ($N = 4$), pyrexia ($N = 3$), infusion-related reaction ($N = 1$), fluid overload ($N = 1$), and ECG T-wave inversion ($N = 1$). Thus, most drug-related serious AEs pertained to infusion-related reactions that were generally limited to the initial infusion. In addition, 1 patient experienced hypotension (grade 2) following premedication. This patient did not receive BI-505 and was not included in the study's safety evaluation. Treatment-related AEs categorized as infections were only reported in 2 patients: impetigo and unspecified infection, both severity grade 2.

### Pharmacokinetics, pharmacodynamics, and immunogenicity

The PK parameters for the first dose in cohorts 8 to 11 (0.9–20 mg/kg) are summarized in Table 4, and observed mean drug concentrations after the first dose for the same cohorts are shown in Fig. 1A. BI-505 concentration data after multiple dosing intervals are shown in Fig. 1B and Table 5. Exposure ($C_{max}$ and AUC) increased with dose; whereas $C_{max}$ increased in a dose-proportional manner between the 0.9 and 20 mg/kg dose groups, AUC increased in a supra-proportional and proportional manner in the

**Table 3.** Treatment-emergent AEs in more than 5% of the study population

| AEs | *n* (%) |
|---|---|
| Overall, treatment-related AE | 26 (76) |
| Pyrexia | 10 (29) |
| Fatigue | 9 (26) |
| Headache | 9 (26) |
| Chills | 8 (24) |
| Nausea | 7 (21) |
| C-reactive protein increase | 5 (15) |
| Diarrhea | 3 (9) |
| Infusion-related reactions | 3 (9) |
| Blood uric acid increase | 2 (6) |
| Flushing | 2 (6) |
| Hemoglobin decrease | 2 (6) |
| Hypertension | 2 (6) |
| Lymphopenia | 2 (6) |
| Thrombocytopenia | 2 (6) |



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**Table 4.** PK parameters after first dose of BI-505, noncompartmental analysis

| Parameter | Unit | 0.9 mg/kg ($N = 3$) | 3 mg/kg ($N = 7$) | 10 mg/kg ($N = 10$) | 20 mg/kg ($N = 3$) |
|---|---|---|---|---|---|
| $AUC_{0-168}$ | µg×h/mL | 34.1 (276) | 1,830 (37.4) | 6,770 (175) | 23,200 (9.89) |
| $AUC_{0-t}$ | µg×h/mL | 34.1 (276) | 1,920 (39.8) | 8,220 (195) | 33,400 (9.87) |
| $AUC_{0-\infty}$ | µg×h/mL | 34.0 (277) | 1,920 (39.8) | 8,600 (201) | NC |
| $C_{max}$ | µg/mL | 4.32 (40.6) | 49.2 (31.0) | 130 (82.3) | 380 (2.45) |
| $t_{max}$[a] | h | 1.75 (1.50–5.37) | 0.50 (0.483–3.75) | 1.04 (0.500–6.00) | 0.50 (0.500–1.10) |
| $t_{1/2}$[b] | h | 3.56 | 33.1 | 43.8 | NC |
| CL | mL/h/kg | 8.82 (277) | 1.57 (39.8) | 0.93 (64.8) | NC |
| $V_z$ | mL/kg | 71.9 (72.3) | 76.8 (30.3) | 78.3 (49.6) | NC |

Abbreviations: *N*, number of patients in the dose group; NC, not calculated (parameters with ≤3 observations).
[a]$t_{max}$, median (min–max).
[b]$t_{1/2}$, harmonic mean.

0.9–3 and 3–20 mg/kg dose groups, respectively. Following $C_{max}$ at dose levels 10 and 20 mg/kg, the concentration declined in a biexponential pattern: a rapid distribution phase followed by a slow elimination phase. The terminal half-life, based on a non-compartment evaluation, appeared to increase with increasing dosing: 3.6 hours at 0.9 mg/kg compared with 44 hours at 10 mg/kg. The half-life based on a two-compartment fit to multiple doses at the 10 and 20 mg/kg level was in the range of 5 to 11 days, which is similar to the half-life of several other therapeutic monoclonal antibodies. The rapid clearance at low-dose levels suggests target-mediated clearance. The notably slower clearance at dose levels 10 and 20 mg/kg indicates that target-mediated clearance was not an issue at higher dose levels. BI-505 trough levels for all subjects who were dosed with 10 or 20 mg/kg every 14 day were ≥3 µg/mL.

Anti-BI-505 specific antibodies were detected in 3 out of 33 patients analysed already in the pre-dose sample. However, the antibody titres remained either stable or decreased in the following samples and at end-of-treatment, indicating that none of the subjects produced an increased amount of anti-BI-505 antibodies during exposure (not shown).

Saturation of the ICAM-1 BI-505 epitopes on multiple myeloma cells in bone marrow was achieved with the 3, 10, and 20 mg/kg BI-505 doses groups. Previous studies have shown that complete saturation of BI-505 epitopes on multiple myeloma cells is achieved at concentrations around 1 µg/mL. As can be seen in Supplementary Table S1, BI-505 bone marrow concentrations for the 3, 10, and 20 mg/kg cohorts were all >1 µg/mL. The expression of ICAM-1 on bone marrow multiple myeloma cells ranged from 23% to 78% of the screening ICAM-1 expression level 48 hours after the first dose, and ranged from 31% to 88% before infusions 2 (day 15) and 4 (day 43; see Supplementary Table S1). Thus, the ICAM-1 expression on multiple myeloma cells decreased after BI-505 infusions compared to pre-dose levels.

The 10 mg/kg dose of BI-505 was determined to be the optimal biological dose because it was the lowest dose at which serum concentrations were >1 µg/mL (and BI-505 epitopes were saturated) throughout the entire dosing interval (2 weeks).

### Efficacy

In this heavily pretreated patient population, no objective responses were observed during the course of the study. Using the IMWG myeloma response criteria, 7 of the 29 patients (24.1%) treated with 0.09–20 mg/kg had stable disease for at least 2 months (range, 71–169 days; median, 91 days). Three of the 7 patients with stable disease received corticosteroids as premedication (30–40 mg oral prednisolone; 1–11 doses).

## Discussion

Combinations of chemo- and immune-therapy are used successfully in several types of cancer, including lymphomas (6), leukemias (7), and breast cancer (8), where adding a monoclonal antibody to chemotherapy significantly enhances response rate and time to disease progression. There is currently no approved

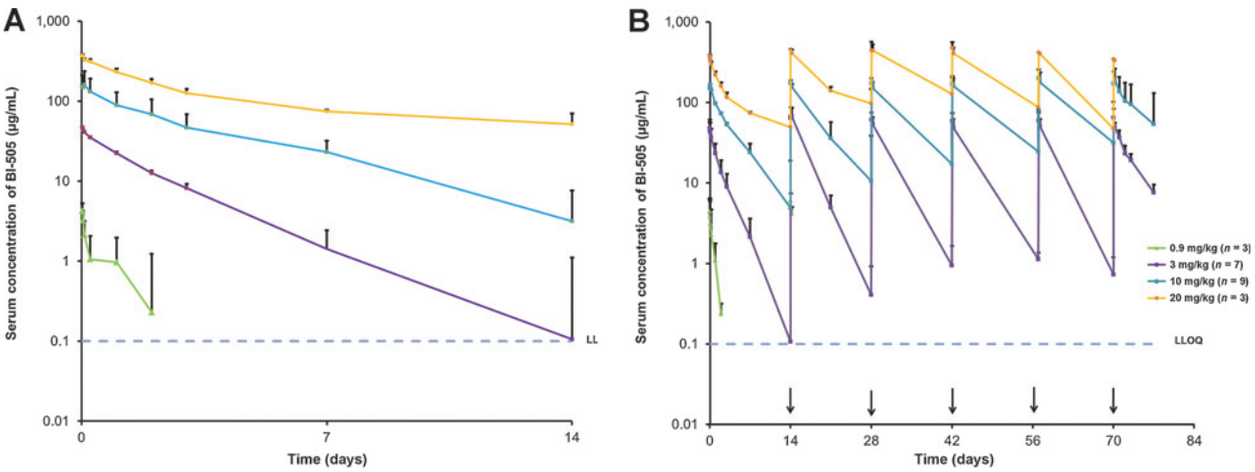


**Figure 1.**
Pharmacokinetics. Observed BI-505 serum concentration versus time curves (mean ± SD) in dose groups from 0.9 mg/kg and higher. A, pharmacokinetics after first dose. B, pharmacokinetics after multiple doses. LLOQ, lower limit of quantification; arrow, BI-505 infusions.



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**Table 5.** PK parameters after multiple doses of BI-505, two-compartmental model

| Parameter | Unit | 10 mg/kg ($N_{obs}$ = 5) | 20 mg/kg ($N_{obs}$ = 3) |
|---|---|---|---|
| $AUC_{0-\infty}$ | μg × h/mL | 14,200 (31.9) | 70,000 (56.9) |
| $C_{max}$ | μg/mL | 179 (43.2) | 479 (12.0) |
| $t_{1/2}$[a] | h | 97.0 (34.3) | 341 (83.2) |
| CL | mL/h/kg | 0.703 (28.4) | 0.286 (43.4) |
| $V_{ss}$ | mL/kg | 89.4 (36.0) | 139 (16.5) |

Abbreviations: CL, total systemic clearance; $N_{obs}$, number of observations used in the calculation; $V_{ss}$, volume of distribution at steady state.
[a]$t_{1/2}$, harmonic mean.

and commercially available therapeutic antibody for multiple myeloma; however, a broad range of monoclonal antibodies with different targets is being tested in clinical trials (9–12), such as CD20 (13), CD56 (14), CD38 (15), CD138 (16, 17), CS-1 (18, 19), IL-6 (20, 21), and RANKL (22). This fact suggests that antibody-therapy will become as important in multiple myeloma as in other cancer treatments. In this study, we demonstrated that the fully human, high-affinity IgG1 anti-ICAM-1 antibody BI-505 is safe and well tolerated when administered to patients with advanced multiple myeloma at doses sufficient to achieve biologically relevant serum concentrations and target saturation. In the 3-mg/kg, 10-mg/kg, and 20-mg/kg dose-cohort, BI-505 infusions resulted in target saturation without DLT. The MTD was not reached in this study with doses up to 20 mg/kg, as only one DLT was observed (in the 3 mg/kg cohort) in this study. The optimal biologic dose was determined to be 10 mg/kg every 2 weeks, based on complete saturation of ICAM-1 epitopes on bone marrow multiple myeloma cells during the entire dosing interval.

Reversible infusion-related reactions were commonly experienced within 24 to 48 hours after initial exposure to BI-505 in the higher dosing groups. Common signs and symptoms of infusion-related reactions included pyrexia, chills, headache, and elevated CRP. To counter these reactions, a premedication regimen consisting of corticosteroids, antihistamine, and acetaminophen/paracetamol was implemented to the highest dose groups before the initial infusion of BI-505, and before subsequent cycles if necessary. In addition, the infusion rate was reduced at the higher doses during the first infusions. AEs reported in this study did not increase in a dose-proportional manner, which may be due to adjustment of the dosing regimen over time (addition of premedication and reduction in initial infusion rate).

In addition to the infusion-related reactions, other common treatment-related AEs included fatigue, nausea, and diarrhea, as well as various hematologic or other serum chemistry laboratory abnormalities. Most of the clinically significant laboratory abnormalities encountered in the study were consistent with the patient's multiple myeloma disease state. The CRP elevations appeared to be associated with infusion-related reactions, most likely due to cytokine release.

No objective responses were observed in this heavily pretreated patient cohort. However, 7 patients had stable disease for more than 8 weeks. In preclinical murine models BI-505's efficacy was shown to be macrophage-dependent (5), and was improved when combined with bortezomib (23) and lenalidomide (24), arguing for further exploration of BI-505 in combination with macrophage stimulation (25–27) or with antimyeloma therapy. Furthermore, these observations indicate that BI-505 will be most efficacious in patients with less impaired immune function and lower tumor burden and in combination with nonmyelosuppressive agents such as lenalidomide and bortezomib, for example as maintenance therapy after high-dose melphalan treatment with autologous stem-cell transplant or after having achieved a very good partial response with nontransplant therapies. This will be further explored in coming clinical trials. An ongoing trial investigates BI-505 efficacy in smoldering myeloma (www.clinicaltrials.gov, NCT01838369).

## Disclosure of Potential Conflicts of Interest

B. Frendeus has ownership interest (including patents) in BioInvent International AB. No potential conflicts of interest were disclosed by the other authors.

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