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Elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma: final phase 2 results from the randomised, open-label, phase 1b–2 dose-escalation study

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PGR, SJ, JZ, LCT, KCA, AKS, and SL participated in study design. PGR, PM, AJJ, and TF collected, analysed, and interpreted the data. MSR, DW, DER, LB, and JZ also collected data; SJ, KCA, EB, AKS, and SL also analysed the data. MSR, DW, LB, and JZ helped to interpret the data. SJ, RV, JZ, KCA, and SL participated in patient enrolment, and MSR and LB helped to recruit them. RV was involved in consenting and treating patients in the trial. LCT participated in statistical analyses. EB participated in the interpretation of the clinical protocol and the overall clinical development of the molecule. AKS oversaw the development of the molecule, including development of the clinical protocol; participated in the execution of the actual clinical study; and reviewed the data. All authors contributed to the writing of the report, reviewing it for intellectual content, and approved the submitted version.

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Declaration of interests

PGR reports serving on the advisory committee for Bristol-Myers Squibb and Celgene. SJ reports consulting for Bristol-Myers Squibb and Celgene. AJJ reports institutional funding from Bristol-Myers Squibb for support of clinical trial conduct; and personal fees (advisory board, consultancy, speaking, and honoraria) from Bristol-Myers Squibb, Celgene, Millennium, Novartis, Onyx, SkylineDx, Karyopharm, and Sanofi-Aventis. TF reports personal fees from Bristol-Myers Squibb and Celgene. RV reports consulting for Bristol-Myers Squibb and Celgene. DW reports grants from Bristol-Myers Squibb, and grants or personal fees from Celgene, Janssen, Novartis, Amgen, and Takeda. DER reports consulting fees from Celgene and Janssen, and fees for lectures including speakers' bureaus from Janssen, Celgene, Novartis, and Amgen. LB reports research honoraria from Bristol-Myers Squibb, Millennium, Onyx Therapeutics, and Lilly; and consultancy, advisory board membership, travel expenses, and research honoraria for and from Celgene. JZ reports research funding from Celgene, serves on the data and safety monitoring committee for Pharmacyclics consultancy, and reports personal fees (steering committee, consultancy, and advisory board participation) from Celgene, Prothena, Bristol-Myers Squibb, Onclave, and Array Biopharma. LCT and AKS report employment at AbbVie Biotherapeutics. KCA reports consulting for Celgene, Millennium, Gilead, Sanofi-Aventis, and Bristol-Myers Squibb, and serving as scientific founder of Oncopep and Acetylon. EB reports employment at Bristol-Myers Squibb. SL reports personal fees (consultancy or advisory role) for Millennium, Celgene, Novartis, Bristol-Myers Squibb, Onyx, and Janssen. PM and MSR declare no competing interests.

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Summary

Background—Elotuzumab, an immunostimulatory monoclonal antibody targeting signalling lymphocytic activation molecule (SLAM) family member 7 (SLAMF7), selectively kills SLAMF7-expressing myeloma cells through direct activation and engagement of the innate immune system, and thus might have clinical benefit in the treatment of myeloma. In phase 1 of this phase 1b–2 study, 82% of patients with relapsed multiple myeloma who were given elotuzumab plus lenalidomide and dexamethasone achieved an overall response. Here we report the final phase 2 results.

Methods—We did this randomised, multicentre, open-label, dose-escalation study (1703) at 17 hospitals in the USA, Canada, France, and Germany. Patients aged at least 18 years with confirmed, relapsed multiple myeloma, Eastern Cooperative Oncology Group performance status 0–2, and one to three previous therapies but no previous lenalidomide were eligible for phase 2. We randomly assigned patients (1:1) to either 10 mg/kg or 20 mg/kg intravenous elotuzumab plus oral lenalidomide (25 mg) and dexamethasone (40 mg). We stratified patients on the basis of the number of previous therapies (one versus two or three), and status of previous treatment with immunomodulatory drugs (yes or no), and used permuted block randomisation with a block size of four. Treatment was given in 28-day cycles until disease progression or unacceptable toxic effects occurred (elotuzumab was given on days 1, 8, 15, and 22 for cycles 1 to 2 and days 1 and 15 for subsequent cycles; lenalidomide was given on days 1–21 and dexamethasone once per week). The primary endpoint was the proportion of patients who achieved an objective response according to International Myeloma Working Group criteria. Primary analyses were done in the intention-to-treat population, and safety was analysed in all patients who received at least one dose of study drugs. This study is registered with ClinicalTrials.gov, number .

Findings—Between Jan 4, 2010, and Dec 21, 2010, we recruited and randomly assigned 73 patients to elotuzumab (36 to 10 mg/kg, 37 to 20 mg/kg). At data cutoff (Jan 16, 2014), 13 patients remained on treatment (six on 10 mg/kg, seven on 20 mg/kg). 61 (84%) patients achieved an objective response (33 [92%] with 10 mg/kg, 28 [76%] with 20 mg/kg); 31 (42%) a very good partial response (17 [47%] with 10 mg/kg, 14 [38%] with 20 mg/kg); and 20 (27%) a partial response (10 [28%] with 10 mg/kg, 10 [27%] with 20 mg/kg). The most common treatment-emergent adverse events of any grade were diarrhoea (48 [66%]), muscle spasms (45 [62%]), and fatigue (41 [56%]). 57 (78%) patients had grade 3–4 events, the most common of which were lymphopenia (15 [21%]) and neutropenia (14 [19%]). Three deaths occurred, none related to the study drugs.

Interpretation—Elotuzumab combined with lenalidomide and dexamethasone in patients with relapsed multiple myeloma showed acceptable safety and efficacy that seems better than that previously noted with lenalidomide and dexamethasone only. Phase 3 trials are in progress.

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Introduction

Multiple myeloma is a progressive haematological cancer characterised by uncontrolled proliferation of malignant plasma cells in the bone marrow and aberrant production of an abnormal IgM protein.[1,2] Several new therapies have emerged,[3,4] leading to an improvement in both overall survival and time to relapse, particularly in patients younger than 75 years.[5] Advances in therapy include immunomodulatory agents, proteasome inhibitors, and autologous stem cell transplantation.[6] Importantly, combination regimens have optimised patient outcomes.[7–10] However, despite the increasing number of new treatment options, the probability of relapse and eventual development of refractory disease is high.[11,12] Thus, strategies incorporating treatments with novel mechanisms of action are increasingly important. Although immunotherapeutic agents, including monoclonal antibodies, have shown clinical benefit in solid tumours and other haematological malignancies,[13–15] none have yet established clinical benefit in the treatment of myeloma.

Elotuzumab is a humanised IgG1 (IgGκ) monoclonal antibody targeted against signalling lymphocytic activation molecule (SLAM) family member 7 (SLAMF7), a glycoprotein expressed on myeloma cells and on natural killer cells, but not on other healthy tissues. SLAM is a subset of the immunoglobulin superfamily of receptors and consists of six members.[16] More than 90% of bone marrow samples from patients with multiple myeloma express SLAMF7.[2] Elotuzumab works via a novel immunotherapeutic dual mechanism of action by both directly activating natural killer cells and through antibody-dependent cell-mediated cytotoxicity, via the CD16 pathway to cause targeted, SLAMF7-positive, myeloma-cell death.[17] SLAMF7 mediates activating signals in natural killer cells by coupling to its adaptor protein EAT-2; elotuzumab does not induce myeloma cell proliferation.[18]

In preclinical development, elotuzumab showed substantial in-vivo efficacy in mouse xenograft models of multiple myeloma.[1,2] Furthermore, elotuzumab in combination with different classes of agents (including pretreatment with dexamethasone or agents such as bortezomib, lenalidomide, Akt inhibitors, or MEK inhibitors) has been shown to enhance antibody-dependent cell-mediated cytotoxicity in vitro.[1,19,20] The synergistic effect of combination therapy is thought to be mediated by enhancement of natural killer cell activity.[21] Besides modulating natural killer cell function, the combination of lenalidomide and elotuzumab has been shown to increase the expression of CD25 and CD54 on natural killer cells.[22] In phase 1 clinical trials, elotuzumab was well tolerated, with a favourable pharmacokinetic profile.[1,2,23] Additionally, antidrug antibodies and neutralising antibodies —widely observed occurrences in the development of therapeutic antibodies[24]—were not shown to correlate with adverse events, response, or disease progression.[23]

Our phase 1b–2 1703 trial investigated the combination of elotuzumab with lenalidomide and dexamethasone in patients with relapsed multiple myeloma; the phase 1 results have been previously published.[25] During the phase 1 dose-escalation portion of the trial, no dose-limiting toxicities were noted in the 5, 10, or 20 mg/kg cohorts. Results from pharmacokinetic analysis showed a steady-state elotuzumab serum concentration of more than 70 μg/mL with both 10 and 20 mg/kg, consistent with the optimum antitumour

concentration in the preclinical model.[25] Objective responses were obtained in 23 (82%) of 28 patients. At the time of data cutoff (Aug 20, 2010) for publication of the phase 1 data, median time to progression had not been reached after 16·4 months of follow-up in the 20 mg/kg cohort.

On the basis of the initial safety profile and durable efficacy noted in phase 1b, we did this phase 2 extension to further assess the treatment benefits of elotuzumab with lenalidomide and dexamethasone and to identify the optimal dose of elotuzumab in patients with relapsed multiple myeloma. Methods and initial results of the phase 1 portion have been previously reported.[25] Here we present updated data from the phase 1 cohort and methods and data from the phase 2 extension, which assessed the efficacy of elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma after one to three previous therapies. The primary objective of this phase 2 study was to assess the efficacy. Our secondary objectives were to assess the safety and immunogenicity of elotuzumab and its tolerability at an infusion rate of up to 5 mL/min.

Methods

Study design and patients

1703 was a phase 1b–2, multicentre, randomised, open-label, dose-escalation study that we did at 17 hospitals across the USA, Canada, France, and Germany (appendix p 3). The study protocol was approved by the ethics committee at every centre and the study was done in accordance with Good Clinical Practice and the Declaration of Helsinki.

Key inclusion criteria for participants in this phase 2 part of the study were: aged at least 18 years with a confirmed diagnosis of multiple myeloma, Eastern Cooperative Oncology Group performance status 0–2, one to three previous lines of therapy (in phase 1, patients with at least one previous line of therapy were eligible), evidence of disease progression since, or refractory to, the most recent previous treatment, and disease measurable via the M-protein component in serum or urine. Key exclusion criteria included previous lenalidomide therapy (previous lenalidomide was allowed in phase 1), previous malignant diseases (except for adequately treated basal cell or squamous cell skin cancer, in-situ cervical cancer, or other cancer from which the patient had been disease free for at least 2 years), active or previous plasma cell leukaemia, or peripheral neuropathy of grade 3 or higher. Additionally, patients were excluded if they had received thalidomide, bortezomib, corticosteroids, cytotoxic chemotherapy, or any investigational drugs during the 2 weeks before initiation of elotuzumab; previous peripheral stem cell transplantation (up to 12 weeks beforehand), or nitrosoureas (up to 6 weeks beforehand). Previous and concomitant drugs are listed in the appendix (p 1). All patients provided written informed consent before participating in the study.

Randomisation and masking

We assigned patients (1:1) to receive either elotuzumab 10 mg/kg or 20 mg/kg in combination with lenalidomide and dexamethasone. We stratified patients based on the number of lines of previous therapies for multiple myeloma (one versus two or three) and

status of previous treatment with immunomodulatory drugs (yes or no). The ratio of treatment assignments was maintained within each of the strata. We used permuted block randomisation with block sizes of four, which took place across all study sites with a centralised web and telephone interactive voice response system (IVRS). The random assignment sequence was generated by Phase Forward/Clarix, and patients were entered at the investigator sites using IVRS to randomly assign treatment. No masking was necessary because this was an open-label study.

Procedures

Treatment was given in 28 day cycles until disease progression or unacceptable toxic effects occurred. We gave intravenous elotuzumab (10 or 20 mg/kg) on days 1, 8, 15, and 22 for cycles 1 to 2 and on days 1 and 15 for subsequent cycles. Patients also received 25 mg of lenalidomide on days 1–21 and 40 mg of dexamethasone once per week (figure 1).

During phase 1b, if we identified infusion reactions we sequentially modified the premedication regimen to mitigate their incidence and severity. In phase 2, we gave this premedication regimen to each patient before infusion of elotuzumab. The regimen included dexamethasone given as a split dose of 28 mg given orally 3–24 h before infusion and 8 mg given intravenously 45 min before infusion, an H_1 blocker (diphenhydramine 25–50 mg orally, intravenously, or equivalent), an H_2 blocker (ranitidine 50 mg intravenously or equivalent), and paracetamol (650–1000 mg orally), all given 30 to 90 min before infusion. Elotuzumab (both 10 and 20 mg/kg) was infused at up to 2 mL/min in cycles 1 to 4 and could be escalated up to 5 mL/min (duration <1 h) for subsequent cycles in patients who tolerated the lower rate.

In cycle 1, if a patient developed grade 4 thrombocytopenia or neutropenia, or a non-haematological toxic effect of grade 3 or higher that was thought to be related to lenalidomide, dose interruptions of lenalidomide of more than 7 days were allowed. A dose of elotuzumab or dexamethasone could be withheld for more than 7 days if a patient had an adverse effect of grade 3 or higher that was related to either drug. From cycle 2 onwards, treatment with one or more study drugs could be delayed for no more than 28 days.

Withdrawal criteria from the study were: any adverse event (serious or non-serious), drug reaction, or complication—whether related or not to study drugs—which precluded continuation of elotuzumab treatment; a dose-limiting toxic effect during dose escalation in the phase 1 portion of the study; a grade 4 elotuzumabrelated infusion reaction during the phase 2 portion; pregnancy; starting an alternative multiple myeloma treatment; non-compliance; disease progression as per International Myeloma Working Group (IMWG) criteria;[26] being lost to follow-up; at the decision of the patient; and if the principal investigator deemed it not in the patient's best interest to continue. To test for pregnancy, negative urine pregnancy tests were required for females of child-bearing potential at screening and before prescribing lenalidomide. Females of child-bearing potential with regular or no menstrual cycles had to agree to have pregnancy tests every week for the first 28 days of study participation, every 28 days while in the study, at study discontinuation, and on day 28 after discontinuation from the study.

Objective responses and disease progression were assessed by the investigators in each treatment cycle according to IMWG criteria.[26] In this study, we did not attempt to distinguish elotuzumab from M-protein detection for determination of complete response. We did plasma cell myeloma karyotyping via standard karyotyping or fluorescence in-situ hybridisation assay, according to published criteria.[27]

We assessed antidrug antibodies using a tiered electrochemiluminescent assay strategy. Positive samples were titrated to establish the strength of response, then tested in the confirmatory assay. We analysed confirmed positive samples using drug-depleted samples in a cell-based neutralising antibody assay. Elotuzumab-specific antidrug antibodies, neutralising antibodies, and the frequency of antidrug antibody development were assessed before infusion (pre-existing antidrug antibodies) on cycle day 1 and postinfusion (treatment-emergent antidrug antibodies) on cycle day 28, for each cycle. Persistent neutralising antidrug antibodies were recorded if both antidrug antibodies and neutralising antibodies were confirmed positive at more than one timepoint or at the last timepoint, or both.

We monitored treatment-emergent adverse events and serious adverse events from consent until 60 days after the last dose of any study drug. Monitoring and recording of vital signs and clinical or haematological laboratory measurements were done after each treatment cycle. All adverse events were graded by the investigators according to frequency, severity, and relation to study drugs and drug combinations. An independent safety reviewer, not involved with undertaking this study, also reviewed all events, whether they were related or unrelated to the study drugs, on a monthly basis, until protocol amendment G of the study (implemented May 23, 2012), under which data monitoring committee oversight was discontinued. The safety of elotuzumab was then monitored by Bristol-Myers Squibb and Abbott. All enrolled patients were followed-up once every 3 months for safety, and survival and disease status, irrespective of disease progression or initiation of new therapy, until death or study completion.

Infusion-related adverse events were defined as any sign or symptom that occurred within 24 h of giving elotuzumab that the treating physician regarded as being related to elotuzumab and was consistent with the clinical pattern of hypersensitivity reactions noted with other monoclonal antibodies. The occurrence and severity of all such events were identified and recorded by the investigators. If an elotuzumab infusion-related reaction of grade 2 or higher occurred, the infusion was interrupted and the patient was treated as clinically indicated. When the reaction resolved to grade 1 or lower, the infusion was restarted at 0·5 mL/min. If symptoms did not recur after 30 min, the infusion rate was increased in a stepwise method (0·5 mL every 30 min) up to the previously tolerated maximum rate.

Outcomes

The primary efficacy endpoint for the phase 2 portion of the study was the proportion of patients who achieved an objective response according to IMWG criteria.[26] Key secondary endpoints included progression-free survival; objective response per IMWG criteria for phase 1 only; frequency, severity, and relation of adverse events and serious adverse events to treatment; occurrence and severity of infusion-related adverse events; pharmacokinetic

profile; duration of response; incidence of elotuzumab-specific antidrug antibodies; plasma cell myeloma cytogenetic subtype; and changes in pharmacodynamic variables as they relate to dose, response, and toxicity of elotuzumab in combination with lenalidomide and dexamethasone.

Statistical analysis

We planned a sample size of 30 patients per group to provide a two-sided 95% CI with width less than 40% between the lower limit and the upper limit for each dose group, using the Clopper-Pearson (exact) method. This proof-of-concept study did not have a control group and was not designed or powered for direct comparisons between the two dose groups. We did not form a hypothesis for a formal statistical comparison, except to explore the efficacy and safety of both the 10 mg/kg and 20 mg/kg doses of elotuzumab with a historical control as reference.

The following analysis populations were defined: the intention-to-treat population consisted of all patients who had been randomly assigned to treatment, and the safety population consisted of all patients who had received at least one dose of study drug. All randomly assigned patients were given study drugs and included in all analyses. We used the Clopper-Pearson (exact) method to calculate 95% CIs for the proportion of patients who achieved an objective response. We estimated progression-free survival using the Kaplan-Meier product-limit method and expressed it as a median value with range and 95% CIs. The censoring rules for the progression-free analysis for patients who did not progress or die were: (1) withdrew from study early before progression or death; (2) started a new line of multiple myeloma therapy before progression or death; or (3) was still continuing with treatment at the time of data cutoff. These patients were censored at the last IMWG assessment date before they left the study or took the alternative drug. A patient was censored on day 1 if there was no post-baseline IMWG assessment.

We summarised all other secondary endpoints using counts and proportions. All data were analysed on the basis of a data cutoff date of Jan 16, 2014. We did the analyses with SAS version 9.2. An independent data monitoring committee was responsible for the oversight of safety and ethics of this study up until amendment G, when it was recommended by the committee that oversight was no longer necessary. Amendments to the protocol were approved by the institutional review board, independent ethics committee, and local regulatory agency, as appropriate, before the implementation of changes. This trial is registered with ClinicalTrials.gov, number .

Role of the funding source

The funders of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Results

102 patients in total (29 in phase 1[25] and 73 in phase 2) were recruited and enrolled. Between Jan 4, 2010, and Dec 21, 2010, we randomly assigned all 73 patients recruited for phase 2 to receive elotuzumab 10 mg/kg (n=36) or 20 mg/kg (n=37; figure 2). Demographic characteristics were well balanced between groups (table 1); however, slightly more patients had International Staging System stage III disease in the 20 mg/kg group than in the 10 mg/kg group. Four patients were classified as having high-risk cytogenetics under the assessment criteria adopted in phase 2 (appendix p 2).

The phase 2 portion of the study was completed in January, 2014, and data cutoff was on Jan 16, 2014. The patients remaining in the study are either still receiving treatment (13 [18%] of 73 for the phase 2 portion) or in safety follow-up (two [3%] of 73), with assessments at 30 and 60 days after last study dose. Patients were exposed to elotuzumab for a median of 17·0 (range 1–51) treatment cycles (table 2). The median duration of elotuzumab treatment was longer for the 10 mg/kg group than for the 20 mg/kg group. The median number of cycles for the 13 phase 2 patients still receiving treatment in the study as of data cutoff was 48. The relative median dose intensities were 96% for elotuzumab, 77% for lenalidomide, and 75% for dexamethasone. Reductions in elotuzumab dose were not allowed; however, ten (14%) of 73 patients had interrupted or delayed infusions, three (4%) because of an adverse event. Of 73 patients, lenalidomide dose was reduced (on ≥1 occasions) in 43 (59%) and dexamethasone dose was reduced (on ≥1 occasions) in 34 (47%). The total number of elotuzumab infusions given throughout the study was 3412; 1127 (33%) of these were given at 5 mL/min. 31 (42%) of 73 patients were given one or more elotuzumab infusions that included the highest planned rate of 5 mL/min.

At data cutoff, of the 28 treated patients from the phase 1 cohort, 23 (82%; 95% CI 63·1–93·9) had an overall response, unchanged from the previously published phase 1 portion.[25] Median duration of follow-up was 11·3 months (range 2·3–58·9). The best overall response was complete response for one (4%) of 28 patients, very good partial response for 12 (43%), and partial response for ten (36%). Median progression-free survival was 32·9 months overall (95% CI 7·43–not available; appendix p 4).

Of the 73 patients across both treatment groups in the phase 2 cohort, 61 (84%, 95% CI 73·0–91·2) had an objective response (table 3). The best overall responses are also shown in table 3. We did an exploratory analysis of response by risk group; among patients with high-risk disease (n=4), all achieved a partial response or better. 44 (81%) of 54 patients with standard-risk disease and four (80%) of five patients with low-risk disease achieved a partial response or better. The median time to first response was 1·0 months overall (range 0·7–19·2): 1·0 months (0·8–4·2) for the 10 mg/kg group and 1·7 months (0·7–19·2) for the 20 mg/kg group. The median time to reach best overall response was 2·6 months overall (range 0·7–33·0): 2·8 months (0·8–33·0) in the 10 mg/kg group and 2·4 months (0·7–24·7) in the 20 mg/kg group. The median duration of response with Kaplan-Meier estimates was 29·2 months overall (IQR 14·1–not estimable [NE]): 34·8 months (12·7–NE) for the 10 mg/kg group and 29 months (15·1–NE) for the 20 mg/kg group. For all patients, the median

duration of follow-up was 21·2 months (range 3·9–45·8) for the 10 mg/kg group and 16·8 months (2·1–47·2) for the 20 mg/kg group.

Progression-free survival is shown in figure 3. The median duration of follow-up for censored patients was 37·0 months (IQR 11·1–41·2) for the 10 mg/kg group (n=19) and 12·0 months (2·8–43·7) for the 20 mg/kg group (n=18). Responses were noted in high-risk patients (n=4, as defined by IMWG criteria;[27] appendix). The one high-risk patient on 10 mg/kg had a duration of response of 253 days. Three high-risk patients in the 20 mg/kg group had durations of response of 90, 275, and 883 days, respectively.

In the phase 2 portion of the study, we noted no clinically meaningful differences in safety between the 10 mg/kg and 20 mg/kg groups (table 4). The most common adverse events of any grades were diarrhoea, muscle spasms, fatigue, constipation, nausea, upper respiratory tract infections, pyrexia, and back pain. Grade 3 or 4 treatment-emergent adverse events were reported in around three-quarters of patients; those reported in at least 10% of patients overall were lymphopenia, neutropenia, thrombocytopenia, and anaemia. 13 (18%) of 73 patients discontinued from the study because of treatment-emergent adverse events. (One of these 13 patients discontinued because of bone pain, which was most probably caused by disease progression and therefore the primary reason for discontinuation was classed as disease progression by the investigator.) The most common reasons for discontinuation were sepsis (two [3%] patients) and myelodysplastic syndrome (two [3%] patients). Of the two patients who developed myelodysplastic syndrome, one was a man aged 74 years who had received 1·5 years of oral melphalan–prednisone and 6 months of bortezomib before treatment with elotuzumab plus lenalidomide and dexamethasone. The other patient was a woman aged 69 years who had received thalidomide for more than 1 year, had undergone an autologous stem-cell transplantation, and received 1 year of carfilzomib before treatment with elotuzumab plus lenalidomide and dexamethasone. Phase 1 safety results have been previously reported.[25]

Three deaths were reported, caused by sepsis in two (3%) patients (concurrent with cellulitis, pneumonia, and multiorgan failure in one of the two patients) and by renal failure in a third patient. None were designated by the investigators as being related to elotuzumab treatment. Second primary malignancies were reported in eight (11%) of 73 patients, namely two myelodysplastic syndrome, malignant melanoma, prostate cancer, bladder transitional cell carcinoma, squamous cell carcinoma, squamous cell carcinoma of the skin, and basal cell carcinoma, none of which were thought by the investigators to be related to elotuzumab.

To identify potential high-grade adverse events that could occur because of chronic dosing with elotuzumab, treatment-emergent adverse events were reviewed after 24 months of treatment. Of the 30 patients still on treatment (17 on 10 mg/kg, 13 on 20 mg/kg) at this time (table 5), grade 3 or 4 adverse events reported in at least 5% of patients were diarrhoea, neutropenia, anaemia, dyspnoea, syncope, and pneumonia. No new safety signals were recorded after 2 years.

Investigator-designated infusion reactions were reported in eight (11%) of 73 patients, with one (1%) grade 3 infusion reaction (rash, leading to treatment discontinuation). Events of

any grade reported in more than one patient were pyrexia and nausea (table 6). One grade 1 or 2 infusion reaction (nausea) and no grade 3 or 4 infusion reactions were noted at flow rates greater than 2 mL/min (table 6). None of the patients who enrolled after the revised premedication regimen was finalised, during phase 2 of the study, had an infusion reaction.

We noted persistent neutralising antidrug antibodies in two (6%) of 36 patients in the 10 mg/kg group and one (3%) of 37 patients in the 20 mg/kg group, all of whom had a best overall response of a partial response. Transient positive results for both antidrug antibodies and neutralising antibodies were reported for three (8%) of 36 patients in the 10 mg/kg group and one (3%) of 37 patients in the 20 mg/kg group. Four patients (one [3%] of 36 with 10 mg/kg, three [8%] of 37 with 20 mg/kg) had pre-existing antidrug antibodies and neutralising antibodies. Of the eight (11%) patients with transient neutralising antidrug antibodies, three (38%) had an infusion reaction of grade 1–3, one of whom (with grade 1 maculopapular rash) was consequently discontinued from the study by the study investigator. One patient with neutralising antidrug antibodies presented with a grade 3 treatment-emergent adverse event (rash) at the same time. None of the patients with a pre-existing anti-elotuzumab response developed a postdose antidrug antibody response.

Discussion

Elotuzumab, a novel immunotherapeutic antibody, shows clinical efficacy in patients with relapsed multiple myeloma at both 10 mg/kg and 20 mg/kg doses in combination with lenalidomide and dexamethasone, possibly due to activation of the innate immune system to selectively kill myeloma cells. This combination provided clinically meaningful benefit in these patients, as measured by the proportion of patients who achieved an overall response, with more than half of patients showing a high-quality response (stringent complete response, complete response, or very good partial response). The duration of response to treatment and progression-free survival were robust, both at a median of 29 months. Patients with high-risk cytogenetics also had a response after treatment with elotuzumab plus lenalidomide and dexamethasone.

High-quality responses (very good partial responses or better) have previously been associated with improved patient outcomes.[28] Notably, results from previous studies of monoclonal antibodies[29–31] have reported underestimating the occurrence of complete responses with detection of the therapeutic antibody in serum protein electrophoresis and immunofixation assays, suggesting that some patients reported as having a very good partial response in this study might, in fact, have had a complete response. Previous clinical trials using lenalidomide–dexamethasone in patients with relapsed multiple myeloma have shown these agents to have efficacy, with favourable progression-free survival and duration of response to treatment. Historical data[7–9] show about 60% of relapsed and refractory patients achieved an overall response, with a median progression-free survival of 11–13 months for lenalidomide and dexamethasone. In the phase 3 ASPIRE trial,[32] the lenalidomide plus dexamethasone treatment group had a median progression-free survival of 17·6 months (95% CI 15·0–20·6). Despite inherent differences in study designs and patient populations between these previous studies and the present 1703 study, the data reported here show the

possibility of substantially improved treatment outcomes with the addition of elotuzumab to lenalidomide and dexamethasone.

Crosstrial comparisons should be done with caution. In the ASPIRE study[32] of carfilzomib in combination with lenalidomide and dexamethasone, 277 (69·9%) of 396 patients had a very good partial response with a median progression-free survival of 26 months (95% CI 23·3–30·5). Differences in the patterns of response between the studies might be due to differences in the patient populations and the different mechanisms of actions of the two drugs. Immuno-oncology agents typically induce a durable long-term response.[33] Other antibodies for the treatment of multiple myeloma are in early stages of clinical development: eg, daratumumab, a CD38-targeted monoclonal antibody, was associated with an overall response in 73% of the study population in a continuing, open-label, single-arm, phase 1–2 trial in combination with lenalidomide and low-dose dexamethasone in 12 patients with relapsed multiple myeloma.[34]

Elotuzumab, lenalidomide, and dexamethasone were generally well tolerated at all doses studied in our phase 2 trial, and we noted no dose-limiting toxic effects. The most common adverse events (diarrhoea, muscle spasms, fatigue, constipation, and nausea) were the same as those reported in phase 1; thus, tolerability remained in the extended phase 2 portion. The relation between infusion reactions and tumour loads was not systematically analysed; however, initial qualitative analysis suggested that no relation exists. Previous clinical trials have reported an increased risk of second primary malignancies associated with lenalidomide treatment.[35] The occurrence of second primary malignancies in eight (11%) of 73 patients across this phase 1b–2 trial is consistent with the incidence noted in historical lenalidomide trials (7–8%; 18 of 231 patients[36] and 26 of 306 patients,[37] respectively). The occurrence of myelodysplastic syndrome in two (3%) of 73 patients with a median time since diagnosis of 4·5 years is in line with the incidence reported in the literature.[38] We noted few differences in overall toxic effects in our 1703 study compared with historical lenalidomide and dexamethasone trials,[7–9] suggesting that the addition of elotuzumab does not adversely affect tolerability.

The number of investigator-designated infusion reactions in the phase 2 portion of the study was low, occurring in eight (11%) of 73 patients, with one (1%) grade 3 infusion reaction (rash, leading to treatment discontinuation). The successful implementation of the premedication regimen throughout phase 2 showed that infusion reactions can be managed effectively with such regimens. Additionally, giving elotuzumab at an increased infusion rate (up to 5 mL/min) was done safely without any increase in infusion reactions. None of the grade 3–4 reactions were had by patients who had received infusions at the 5 mL/min rate. A phase 2 single-arm study () to assess the safety and tolerability of elotuzumab, given at 5 mL/min in combination with lenalidomide and dexamethasone, in patients with relapsed multiple myeloma is under way. 11 (15%) of 73 patients in our study had confirmed treatment-emergent anti-elotuzumab antibodies and neutralising antibodies, most of which were transient. We noted no association between the presence of antidrug antibodies and either efficacy or treatment-emergent adverse events.

This study was limited by sample size and was not powered to detect any statistical difference in efficacy between the elotuzumab 10 mg/kg and 20 mg/kg groups. Tolerability was generally equivalent between the two doses, with similar occurrences and severity of adverse events, serious adverse events, and infusion reactions. Occurrences of responses and progression-free survival were 1 SLAMF7 on myeloma cells and serum antibody concentrations greater than target levels were noted with both doses.[20,23,25] Pharmacokinetics detailed in the previously published phase 1 portion of this study[25] showed that a minimum elotuzumab serum concentration at steady state was maintained at more than 70 μg/mL (the antibody trough concentrations needed for optimum antitumour activity based on a preclinical mouse model) for both elotuzumab 10 mg/kg and 20 mg/kg. Because of the similarities in tolerability, efficacy, and pharmacokinetics between the two doses, the 10 mg/kg dose has been chosen for further study.

The long-term tolerability and sustained efficacy in this study suggest that this treatment regimen could be a suitable option for continuous therapy in patients with relapsed multiple myeloma, an important issue to consider when optimising therapeutic regimens for each patient.[39] Progression-free survival data support the potential use of this combination for extending the time to the next relapse.

The phase 2 and updated phase 1 data for the 1703 trial strongly support the previously published phase 1 findings in both efficacy and safety, and these combined results support the elotuzumab clinical development programme in multiple myeloma in progress. Because of the favourable efficacy, safety, pharmacokinetics, and target saturation previously noted with the 10 mg/kg dose, this has been used in phase 2 and phase 3 studies. Phase 3 controlled trials assessing the efficacy of elotuzumab (10 mg/kg) in combination with lenalidomide and dexamethasone in patients with multiple myeloma are in progress (ELOQUENT-1 [] and ELOQUENT-2 []). Results of the phase 3 ELOQUENT-2 study in patients with relapsed or refractory multiple myeloma have been reported.[40] In this study, the efficacy and safety of elotuzumab in combination with lenalidomide and dexamethasone was supported in a larger cohort of patients. ELOQUENT-2 reported a median progression-free survival of 19·4 months (95% CI 16·6–22·2) in the elotuzumab group, versus 14·9 months (12·1–17·2) in the control group (hazard ratio for progression or death in the elotuzumab group 0·70 [95% CI 0·57–0·85]; $p<0·001$). We noted several differences between the patient populations in our study and ELOQUENT-2 that might account for the difference in progression-free survival. Most notably, in our study patients were younger, fewer had high-risk cytogenetics, and none had previously been exposed to lenalidomide. The data described in our study examines two dosing regimens of elotuzumab, laying the foundation for the ELOQUENT-2 dosing regimen.

In conclusion, elotuzumab, a monoclonal antibody with a unique immunotherapeutic mechanism of action targeting SLAMF7, has the potential to be an important addition to the multiple myeloma treatment arsenal, for which alternative options with differing mechanisms of action, and the ability to complement existing combination strategies, are urgently needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

We searched PubMed without restrictions for the terms “multiple myeloma” AND “dexamethasone” AND “lenalidomide” in published clinical trials to ascertain the historical use of these agents in the treatment of multiple myeloma. From the results of this search, we identified 40 articles in which lenalidomide and dexamethasone had been assessed as a dual therapy, and in combination with several other novel and established multiple myeloma treatments—eg, cyclophosphamide, bortezomib, elotuzumab, and carfilzomib. In phase 3 trials that used lenalidomide and low-dose or high-dose dexamethasone, clinically meaningful efficacy and acceptable tolerability were noted.

Added value of this study

Previous clinical trials using lenalidomide and dexamethasone (MM-009 and MM010 [high-dose dexamethasone plus lenalidomide] and MM-021 [low-dose dexamethasone plus lenalidomide] and the ASPIRE studies) have shown beneficial treatment outcomes in patients with relapsed multiple myeloma. Historical data in these studies show that 48–67% of relapsed and refractory patients achieved an overall response with a median progression-free survival of 11–18 months for lenalidomide plus dexamethasone. Thus, the efficacy data for our 1703 trial suggest the potential for improved treatment outcomes with elotuzumab, with 61 (84%) of patients achieving an overall response and a median progression-free survival outcome of 28·6 months [95% CI 16·62–43·14]) across treatment groups. When we compared safety data for the 1703 trial with those from previous trials, no new safety signals were reported, and the frequency of treatment-emergent adverse events suggested only an incremental rise in toxicity with this treatment combination. Although differences in the study designs and patient populations were evident between previous trials and the 1703 study, the data reported here show the substantial possibility of improved treatment outcomes, with low added toxicity, with the addition of elotuzumab. The phase 3 ELOQUENT-2 trial of elotuzumab plus lenalidomide–dexamethasone versus lenalidomide–dexamethasone alone (control) showed that 252 (79%) of 321 patients achieved an overall response in the elotuzumab group versus 213 (66%) of 325 in the control group. Additionally, median progression-free survival was 19·4 months (95% CI 16·6–22·2) in the elotuzumab group versus 14·9 months (12·1–17·2) in the control group in relapsed and refractory patients. ELOQUENT-2 was done in a different patient population and in a larger patient cohort than 1703, thus providing additional data to those described here on the use of elotuzumab as an effective treatment regimen for relapsed and refractory patients. Analysis of clinical efficacy for multiple myeloma treatments across all trials, taking into account disease characteristics and previous treatment status (including refractory patients), would be beneficial in determining the best treatment options for each patient.

Implications of all the available evidence

The results of our trial lend support to the previously published findings for both efficacy and safety of elotuzumab, and these combined results support the elotuzumab clinical development programme for multiple myeloma. Elotuzumab, at both 10 mg/kg and 20

mg/kg, combined with lenalidomide and dexamethasone, produced clinically meaningful benefits in terms of overall responses and progression-free survival. This study supports the use of the 10 mg/kg dosing regimen in subsequent studies. Results of the phase 3 ELOQUENT-2 study, which studied elotuzumab 10 mg/kg in combination with lenalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma, showed improved progression-free survival with no incremental toxic effects, compared with lenalidomide and dexamethasone alone. Together, these results suggest that elotuzumab has the potential to be an important addition to the multiple myeloma treatment arsenal.

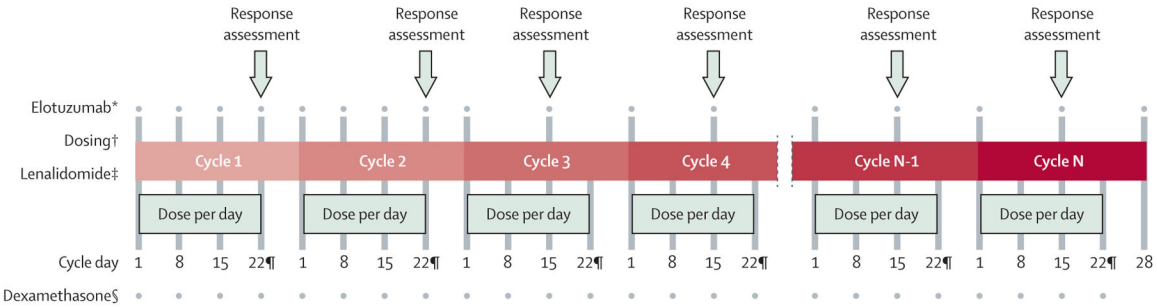

Figure 1: 28-day study treatment schedule

Cycle N-1 refers to the penultimate cycle of treatment. Cycle N refers to the patient's last cycle of treatment.*Elotuzumab given as 10 mg/kg and 20 mg/kg in phase 2. †Drugs were given from −1 to +3 days. ‡Lenalidomide given as 25 mg once per day, from days 1 to 21. §In the weeks with elotuzumab, a split dose of dexamethasone 28 mg was given orally (3–24 h before elotuzumab infusion) and 8 mg intravenously (at least 45 min before infusion); in the weeks without elotuzumab, dexamethasone 40 mg was given orally. ¶In each cycle, days 23 to 28 were rest days (when no study drugs were given).

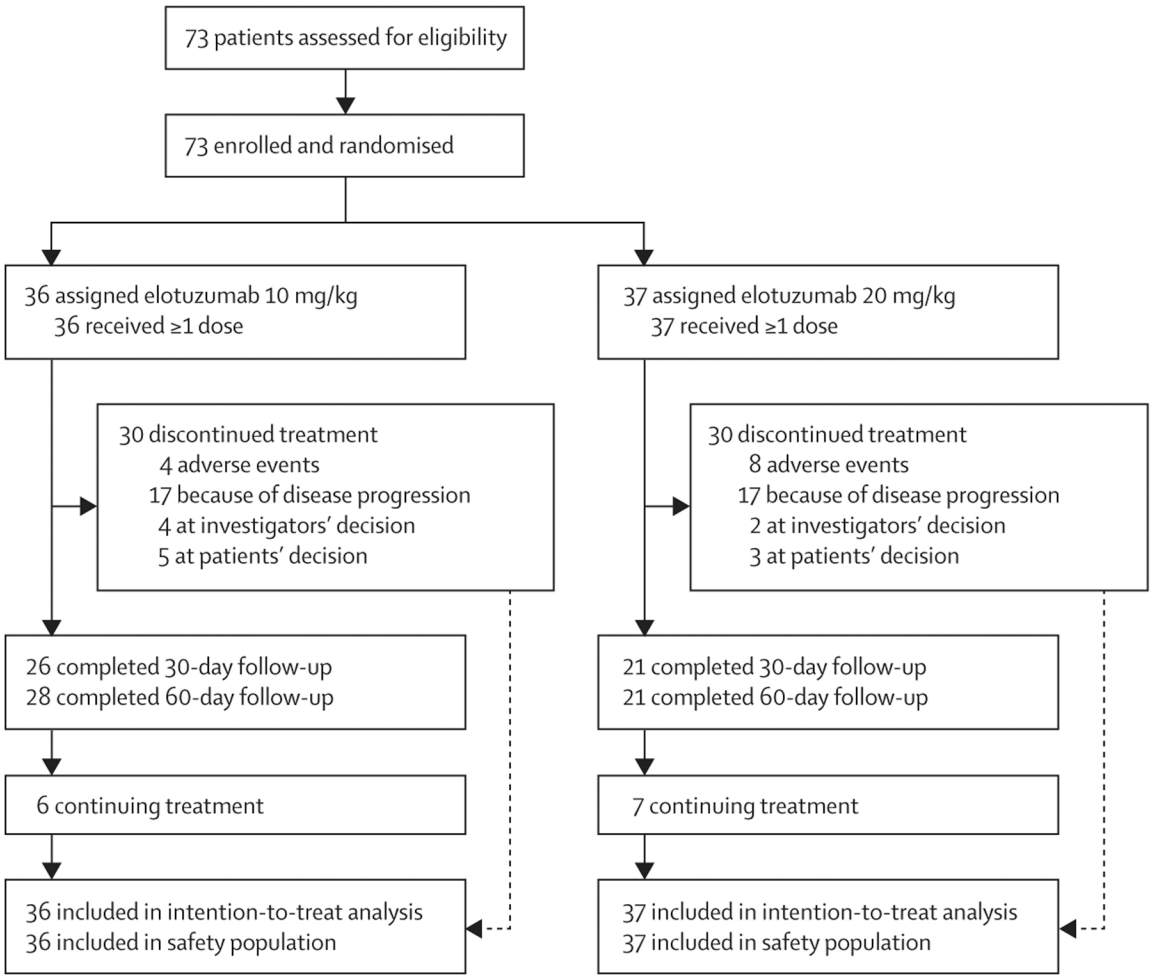

Figure 2:
Trial profile

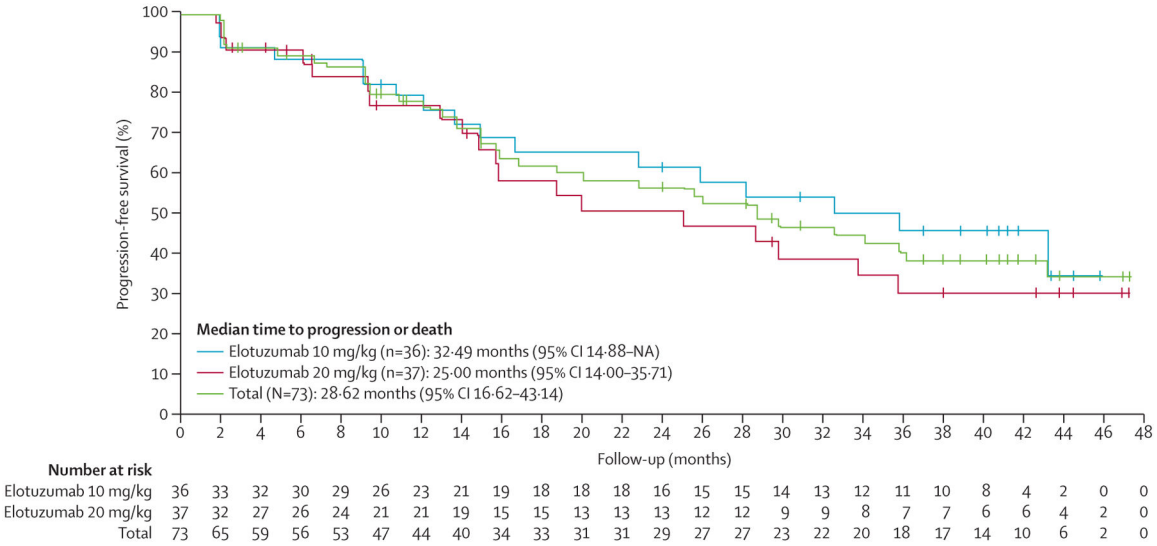

Figure 3: Progression-free survival

NA=not available.

Table 1:

Baseline characteristics of the intention-to-treat population

	Elotuzumab 10 mg/kg (n=36)	Elotuzumab 20 mg/kg (n=37)	Total (N=73)
Sex			
Male	19 (53%)	24 (65%)	43 (59%)
Female	17 (47%)	13 (35%)	30 (41%)
Age (years)	60·6 (9·7), 39–77	63·3 (9·8), 41–82	62·0 (9·8), 39–82
Time since initial diagnosis (years)	4·76 (2·7), 1·2–12·6	4·96 (2·9), 0·7–13·6	4·86 (2·8), 0·7–13·6
Relapses since diagnosis			
One	18 (50%)	21 (57%)	39 (53%)
Two	16 (44%)	14 (38%)	30 (41%)
Three	2 (6%)	2 (5%)	4 (5%)
ISS multiple myeloma stage at study entry *			
I	16 (44%)	9 (24%)	25 (34%)
II	8 (22%)	12 (32%)	20 (27%)
III	11 (31%)	16 (43%)	27 (37%)
Unknown	1 (3%)	0	1 (1%)
Lines of previous therapy			
One	16 (44%)	17 (50%)	33 (45%)
Two	16 (44%)	16 (43%)	32 (44%)
Three	4 (11%)	4 (11%)	8 (11%)
Previous thalidomide	21 (58%)	24 (65%)	45 (62%)
Previous bortezomib	22(61%)	22 (59%)	44 (60%)
Refractory to last treatment †	12 (33%)	12 (32%)	24 (33%)
Refractory to bortezomib †			
Yes	10 (28%)	7 (19%)	17 (23%)
No	12 (33%)	15 (41%)	27 (37%)
Not applicable	14 (39%)	15 (41%)	29 (40%)
Refractory to thalidomide †			
Yes	9 (25%)	5 (14%)	14 (19%)
No	12 (33%)	18 (49%)	30 (41%)
Unknown or not applicable	15 (42%)	14 (38%)	29 (40%)
Previous radiotherapy	4 (11%)	11 (30%)	15 (21%)
Previous transplant	32 (89%)	28 (76%)	60 (82%)
Cytogenetic risk classification ‡			
High	1 (3%)	3 (8%)	4 (5%)
Standard	30 (83%)	24 (65%)	54 (74%)
Low	2 (6%)	3 (8%)	5 (7%)
Not reported	3 (8%)	7 (19%)	10 (14%)
High-risk cytogenetic mutations			
del(17p)	0	2 (5%)	2 (3%)

	Elotuzumab 10 mg/kg (n=36)	Elotuzumab 20 mg/kg (n=37)	Total (N=73)
t(4;14)	1 (3%)	1 (3%)	2 (3%)

Data are mean (SD), range or n (%). ISS=International Staging System.

*Multiple myeloma stage at study entry was not captured in the database for one patient in the 10 mg/kg group.

†Refractory defined as non-responsive while on salvage therapy, or progressing within 60 days of last therapy.

‡High risk represents patients with ISS stage II or III multiple myeloma and t(4;14) or del(17p) abnormality); standard risk represents patients who are not high risk or low risk; low risk represents patients with ISS stage I or II multiple myeloma and absence of t(4;14), del(17p), and 1q21 abnormalities, and aged <55 years. Note that 1q21 was not part of the criteria used in this study to define high-risk patients, therefore these data have not been added. For criteria used in phase 1 compared with phase 2, see appendix p 2.

Table 2:

Elotuzumab treatment and exposure in the intention-to-treat population

	Elotuzumab 10 mg/kg (n=36)	Elotuzumab 20 mg/kg (n=37)	Total (N=73)
Number of treatment cycles	21·5, 3–49	16·0, 1–51	17·0, 1–51
Total duration of study drug (months)	19·1, 1·9–45·8	14·5, <0·1–47·2	14·8, <0·1–47·2
Cumulative dose (mg/kg)	430·4, 86·3–1009·9	711·8, 19·9–2217·8	556·7, 19·9–2217·8
Dose intensity overall (mg/kg per week)	5·3, 3·9–8·2	10·6, 5·0–20·0	8·2, 3·9–20·0
Infusion duration (h)	1·7, 1·2–3·0	3·1, 1·8–4·1	2·3, 1·2–4·1

Data are median, range.

Table 3:

Best responses to elotuzumab plus lenalidomide and dexamethasone in the intention-to-treat population

	Elotuzumab 10 mg/kg (n=36)	Elotuzumab 20 mg/kg (n=37)	Total (N=73)
Overall response *	33 (92%), 77·5–98·2	28 (76%), 58·8–88·2	61 (84%), 73·0–91·2
Best confirmed response †			
Stringent complete response	2 (6%)	1 (3%)	3 (4%)
Complete response	4 (11%)	3 (8%)	7 (10%)
Very good partial response	17 (47%)	14 (38%)	31 (42%)
Partial response	10 (28%)	10 (27%)	20 (27%)
Stable disease	3 (8%)	7 (19%)	10 (14%)
Missing	0	2 (5%)	2 (3%)

Data are n (%), 95% CI. Responses were graded according to International Myeloma Working Group criteria.

*Overall responses comprised stringent complete response, complete response, very good partial response, and partial response.

†Confirmed responses required two or more consecutive assessments of the same response.

Table 4:

Treatment-emergent adverse events in the safety population

	Treatment-emergent adverse event of any grade in ≥20% of patients*			Treatment-emergent adverse event of grades 3 or 4
	Elotuzumab 10 mg/kg (n=36)	**Elotuzumab 20 mg/kg (n=37)**	**Total (N=73)**	**Total (N=73)**
Any grade 3 or 4	32 (89%)	25 (68%)	57 (78%)	57 (78%)
Blood and lymphatic system disorders				
Anaemia	17 (47%)	12 (32%)	29 (40%)	11 (15%)
Lymphopenia	13 (36%)	8 (22%)	21 (29%)	15 (21%)
Thrombocytopenia	13 (36%)	7 (19%)	20 (27%)	13 (18%)
Neutropenia	11 (31%)	8 (22%)	19 (26%)	14 (19%)
Leucopenia	8 (22%)	5 (14%)	13 (18%)	7 (10%)
Eye disorders				
Vision blurred	9 (25%)	3 (8%)	12 (16%)	0
Gastrointestinal disorders				
Diarrhoea	24 (67%)	24 (65%)	48 (66%)	7 (10%)
Constipation	18 (50%)	19 (51%)	37 (51%)	0
Nausea	18 (50%)	17 (46%)	35 (48%)	1 (1%)
Vomiting	10 (28%)	6 (16%)	16 (22%)	1 (1%)
Dyspepsia	8 (22%)	2 (5%)	10 (14%)	0
General disorders and administration-site conditions				
Fatigue	24 (67%)	17 (46%)	41 (56%)	5 (7%)
Pyrexia	14 (39%)	17 (46%)	31 (42%)	2 (3%)
Peripheral oedema	12 (33%)	8 (22%)	20 (27%)	1 (1%)
Asthenia	7 (19%)	12 (32%)	19 (26%)	2 (3%)
Infections and infestations				
Upper respiratory tract infections	19 (53%)	15 (41%)	34 (47%)	2 (3%)
Nasopharyngitis	10 (28%)	9 (24%)	19 (26%)	0
Bronchitis	8 (22%)	9 (24%)	17 (23%)	2 (3%)
Rhinitis	5 (14%)	8 (22%)	13 (18%)	0
Influenza	8 (22%)	2 (5%)	10 (14%)	1 (%)
Metabolism and nutritional disorders				
Hyperglycaemia	9 (25%)	12 (32%)	21 (29%)	7 (10%)

	Treatment-emergent adverse event of any grade in ≥20% of patients*			Treatment-emergent adverse event of grades 3 or 4
	Elotuzumab 10 mg/kg (n=36)	**Elotuzumab 20 mg/kg (n=37)**	**Total (N=73)**	**Total (N=73)**
Decreased appetite	10 (28%)	8 (22%)	18 (25%)	1 (1%)
Musculoskeletal and connective tissue disorders				
Muscle spasms	22 (61%)	23 (62%)	45 (62%)	2 (3%)
Back pain	17 (47%)	13 (35%)	30 (41%)	4 (5%)
Pain in extremity	9 (25%)	12 (32%)	21 (29%)	0
Arthralgia	10 (28%)	8 (22%)	18 (25%)	1 (1%)
Bone pain	4 (11%)	8 (22%)	12 (16%)	2 (3%)
Nervous system disorders				
Dizziness	11 (31%)	7 (19%)	18 (25%)	0
Headache	13 (36%)	5 (14%)	18 (25%)	1 (1%)
Dysgeusia	9 (25%)	6 (16%)	15 (21%)	0
Peripheral neuropathy	8 (22%)	6 (16%)	14 (19%)	0
Psychiatric disorders				
Insomnia	10 (28%)	15 (41%)	25 (34%)	2 (3%)
Respiratory and mediastinal disorders				
Cough	12 (33%)	12 (32%)	24 (33%)	0
Dyspnoea	10 (28%)	10 (27%)	20 (27%)	4 (5%)
Dyspnoea, exertional	9 (25%)	5 (14%)	14 (19%)	0
Skin and subcutaneous tissue disorders				
Night sweats	8 (22%)	10 (27%)	18 (25%)	0
Rash	8 (22%)	9 (24%)	17 (23%)	2 (3%)

Data are n (%). Adverse events listed by preferred terms as defined in the Medical Dictionary for Regulatory Activities, version 16.1. 20% or more patients from either group experienced the adverse events listed in this table (this was not necessarily the case for both groups or overall).

Table 5:

Grade 3 or 4 treatment-emergent adverse events reported before and after 24 months of study drug in the safety population

	≤24 months of elotuzumab*			>24 months of elotuzumab*		
	10 mg/kg (n=36)	**20 mg/kg (n=37)**	**All (N=73)**	**10 mg/kg (n=17)**	**20 mg/kg (n=13)**	**All (N=30)**
≥one grade 3 or 4 event	31 (86%)	25 (68%)	56 (77%)	14 (82%)	4 (31%)	18 (60%)
Lymphopenia	9 (25%)	5 (14%)	14 (19%)	1 (6%)	0	1 (3%)
Neutropenia	6 (17%)	7 (19%)	13 (18%)	2 (12%)	0	2 (7%)
Thrombocytopenia	6 (17%)	6 (16%)	12 (16%)	1 (6%)	0	1 (3%)
Anaemia	4 (11%)	5 (14%)	9 (12%)	2 (12%)	0	2 (7%)
Hyperglycaemia	2 (6%)	5 (14%)	7 (10%)	0	0	0
Leucopenia	3 (8%)	4 (11%)	7 (10%)	1 (6%)	0	1 (3%)
Diarrhoea	3 (8%)	2 (5%)	5 (7%)	3 (18%)	0	3 (10%)
Fatigue	3 (8%)	2 (5%)	5 (7%)	1 (6%)	0	1 (3%)
Pneumonia	3 (8%)	2 (5%)	5 (7%)	0	2 (15%)	2 (7%)
Hypokalaemia	3 (8%)	1 (3%)	4 (5%)	1 (6%)	0	1 (3%)
Back pain	2 (6%)	1 (3%)	3 (4%)	1 (6%)	0	1 (3%)
Syncope	2 (7%)	0	2 (3%)	2 (12%)	0	2 (7%)
Dyspnoea	1 (3%)	1 (3%)	2 (3%)	2 (12%)	0	2 (7%)

Data are number (%). Adverse events listed by preferred terms as defined in the Medical Dictionary for Regulatory Activities, version 16.1.

*Sample sizes used as denominator for percentages.

Table 6:

Investigator-designated infusion reactions in the safety population

	Elotuzumab flow rate ≤2 mL per min		Elotuzumab flow rate >2 mL per min		Total
	Reaction grade 1 or 2	Reaction grade 3 or 4	Reaction grade 1 or 2	Reaction grade 3 or 4	
Pyrexia	3	0	0	0	3
Nausea	1	0	1	0	2
Abdominal pain	1	0	0	0	1
Chest discomfort	1	0	0	0	1
Chills	1	0	0	0	1
Flushing	1	0	0	0	1
Hot flush	1	0	0	0	1
Hyperhidrosis	1	0	0	0	1
Pain	1	0	0	0	1
Periorbital oedema	1	0	0	0	1
Rash	1	1	0	0	1
Rash maculopapular	1	0	0	0	1

Reactions are grouped by elotuzumab infusion flow rate. Adverse events listed by preferred terms as defined in the Medical Dictionary for Regulatory Activities, version 16.1.