Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study

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Summary

Background Belantamab mafodotin (GSK2857916), an immunoconjugate targeting B-cell maturation antigen, showed single-agent activity in the phase 1 DREAMM-1 study in heavily pre-treated patients with relapsed or refractory multiple myeloma. We further investigated the safety and activity of belantamab mafodotin in the DREAMM-2 study.

Methods DREAMM-2 is an open-label, two-arm, phase 2 study done at 58 multiple myeloma specialty centres in eight countries. Patients (aged ≥18 years) with relapsed or refractory multiple myeloma with disease progression after three or more lines of therapy and who were refractory to immunomodulatory drugs and proteasome inhibitors, and refractory or intolerant (or both) to an anti-CD38 monoclonal antibody with an Eastern Cooperative Oncology Group performance status of 0–2 were recruited, centrally randomly assigned (1:1) with permuted blocks (block size 4), and stratified by previous lines of therapy (≤4 *vs* >4) and cytogenetic features to receive 2·5 mg/kg or 3·4 mg/kg belantamab mafodotin via intravenous infusion every 3 weeks on day 1 of each cycle until disease progression or unacceptable toxicity. The intention-to-treat population comprised all randomised patients, regardless of treatment administration. The safety population comprised all patients who received at least one dose of belantamab mafodotin. The primary outcome was the proportion of randomly assigned patients in the intention-to-treat population who achieved an overall response, as assessed by an independent review committee. This study is registered with ClinicalTrials.gov, NCT03525678, and is ongoing.

Findings Between June 18, 2018, and Jan 2, 2019, 293 patients were screened and 196 were included in the intention-to-treat population (97 in the 2·5 mg/kg cohort and 99 in the 3·4 mg/kg cohort). As of June 21, 2019 (the primary analysis data cutoff date), 30 (31%; 97·5% CI 20·8–42·6) of 97 patients in the 2·5 mg/kg cohort and 34 (34%; 23·9–46·0) of 99 patients in the 3·4 mg/kg cohort achieved an overall response. The most common grade 3–4 adverse events in the safety population were keratopathy (in 26 [27%] of 95 patients in the 2·5 mg/kg cohort and 21 [21%] of 99 patients in the 3·4 mg/kg cohort), thrombocytopenia (19 [20%] and 33 [33%]), and anaemia (19 [20%] and 25 [25%]); 38 (40%) of 95 patients in the 2·5 mg/kg cohort and 47 (47%) of 99 in the 3·4 mg/kg cohort reported serious adverse events. Two deaths were potentially treatment related (one case of sepsis in the 2·5 mg/kg cohort and one case of haemophagocytic lymphohistiocytosis in the 3·4 mg/kg cohort).

Interpretation Single-agent belantamab mafodotin shows anti-myeloma activity with a manageable safety profile in patients with relapsed or refractory multiple myeloma.

Funding GlaxoSmithKline.

Introduction

Treatment of patients with relapsed or refractory multiple myeloma remains challenging despite numerous therapeutic advances.[1–6] Patients with disease refractory to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies have a poor prognosis, with newer combination therapies such as selinexor plus dexamethasone resulting in 26% of patients achieving an overall response (median progression-free survival of 3·7 months and median overall survival of 8·6 months).[7] Effective novel therapies with acceptable safety profiles are needed for patients who have exhausted available treatment options.

B-cell maturation antigen (BCMA; also known as TNFRSF17) is a cell-surface receptor that is expressed on multiple myeloma cells, but is virtually absent on naive and memory B cells, making it an ideal therapeutic target.[8,9] Belantamab mafodotin (GSK2857916) is a first-in-class, anti-BCMA immunoconjugate with an afucosylated, humanised IgG1 anti-BCMA monoclonal

Lancet Oncol 2019

Published **Online** December 16, 2019 https://doi.org/10.1016/S1470-2045(19)30788-0

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See Online for appendix

Research in context

Evidence before this study

Effective therapies with acceptable safety profiles are needed to improve outcomes of patients with relapsed or refractory multiple myeloma, particularly for patients with disease that is refractory to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies, who have few treatment options available. Before initiating the DREAMM-1 study, we searched PubMed with the terms "relapsed", "myeloma", "BCMA", and "clinical trial" for studies published from Jan 1, 1990, onwards. Although we identified multiple trials assessing B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor T-cell therapies and related adoptive cellular approaches, we found no published studies in humans of BCMA-targeting antibodies or immunoconjugates. Belantamab mafodotin (GSK2857916) is a first-in-class, anti-BCMA immunoconjugate with a multimodal mechanism of action. In the first-in-human, phase 1 DREAMM-1 study, belantamab mafodotin showed promising anti-myeloma activity, inducing responses in heavily pre-treated patients with relapsed or refractory multiple myeloma.

Added value of this study

DREAMM-2 builds on the results from DREAMM-1, showing that the responses observed with single-agent belantamab mafodotin at both the 2·5 mg/kg and 3·4 mg/kg doses (every 3 weeks) compare favourably with the responses described with other approved treatments in patients who were heavily pre-treated and refractory to immunomodulatory drugs and proteasome inhibitors and refractory or intolerant to anti-CD38 monoclonal antibodies (either alone or in combination). Results from DREAMM-2 also show that the safety profile of belantamab mafodotin is manageable, with no new safety concerns compared to DREAMM-1.

Implications of all the available evidence

Belantamab mafodotin might be a viable treatment option for patients with relapsed or refractory multiple myeloma, particularly those who are refractory to immunomodulatory drugs and proteasome inhibitors, and refractory or intolerant (or both) to anti-CD38 monoclonal antibodies as a single-agent treatment. Additional studies of belantamab mafodotin in combination with standard of care or novel agents are ongoing or planned.

antibody conjugated by a protease-resistant maleimidocaproyl linker to a microtubule-disrupting agent, monomethyl auristatin F (MMAF).[10] Belantamab mafodotin binds to BCMA and kills multiple myeloma cells via a multimodal mechanism, including delivery of MMAF to BCMA-expressing multiple myeloma cells, thereby inducing apoptosis; enhancing antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis; and inducing immunogenic cell death.[10,11] In the first-in-human DREAMM-1 study, single-agent belantamab mafodotin (3·4 mg/kg administered every 3 weeks) induced deep (overall response achieved in 21 [60%] of 35 patients) and durable (median duration of response 14·3 months; 95% CI 10·6–not estimable) responses in patients with heavily pre-treated relapsed or refractory multiple myeloma.[12,13] In a subgroup of 13 patients previously treated with an anti-CD38 monoclonal antibody and refractory to both proteasome inhibitors and immunomodulatory drugs, an overall response was achieved in five (38·5%) patients and median progression-free survival was 6·2 months (95% CI 0·7–7·9).[13]

The DREAMM-2 study was designed to further explore the safety, activity, and clinical benefit profile of two doses of belantamab mafodotin (2·5 mg/kg and 3·4 mg/kg every 3 weeks) in patients with relapsed or refractory multiple myeloma who were refractory to an immunomodulatory drug or proteasome inhibitor, and refractory or intolerant (or both) to an anti-CD38 monoclonal antibody.

Methods

Study design and participants

The open-label, two-arm, phase 2 DREAMM-2 study was done at 58 multiple myeloma specialty centres in eight countries (appendix pp 12–13). Eligible patients with relapsed or refractory multiple myeloma confirmed histologically or cytologically according to International Myeloma Working Group criteria were aged 18 years or older; had an Eastern Cooperative Oncology Group performance status of 0–2; had undergone autologous stem cell transplantation (>100 days before enrolment) or were considered ineligible for a transplant; had disease progression on or after receiving three or more previous lines of anti-myeloma treatments (≥14 days or five half-lives from the last therapy); had adequate organ system function (including sufficient renal function as measured by estimated glomerular filtration rate ≥30 mL/min per 1·73 m²); were refractory to an immunomodulatory drug or proteasome inhibitor, and were refractory or intolerant (or both) to an anti-CD38 monoclonal antibody. Patients with mild to moderate renal impairment and a history of grade 2 cytopenia (without active conditions) were eligible. Additionally, laboratory tests for progressive disease assessment (serology for M-protein and immunoglobulins, urinalysis for M-protein and calcium corrected for albumin, bone marrow biopsy for disease status, and imaging for skeletal lesions), adequate organ function (urinalysis and echocardiography), and pre-existing medical conditions (serology) were required for inclusion. Women had to be of non-childbearing

potential or have a negative serum pregnancy test and use highly effective contraception throughout the study and for at least 80 days after the last dose of study treatment.

Patients with previous BCMA therapies, systemic high-dose corticosteroids, or investigational drugs (≤14 days or five half-lives of treatment); a previous allogeneic stem cell transplant; current corneal epithelial disease (except for mild punctate keratopathy); or any serious or unstable pre-existing medical condition, psychiatric disorder, or any other condition (including laboratory abnormalities) that could interfere with their safety or with obtaining informed consent or compliance with study procedures were excluded. Additional details about inclusion and exclusion criteria are provided in the appendix (pp 2–4).

The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines following approval by ethics committees and institutional review boards at each study site. All patients provided written informed consent. The full study protocol is available in the appendix.

Randomisation and masking

Patients were randomly assigned (1:1) to receive belantamab mafodotin 2·5 mg/kg or 3·4 mg/kg. The 3·4 mg/kg dose was selected as the recommended phase 2 dose on the basis of the clinical activity and safety data observed in DREAMM-1. However, patients receiving this dose often required dose delays and reductions to manage adverse events in DREAMM-1.[12,13] Therefore, to generate additional activity and safety data at the lower dose, both 2·5 mg/kg and 3·4 mg/kg doses were evaluated in DREAMM-2. For this open-label study, randomisation was done centrally by use of interactive response technology, with allocation and stratification based on the number of previous lines of therapy (≤4 *vs* >4) and presence or absence of high-risk cytogenetic features. A centrally generated randomisation schedule with permuted blocks (block size of 4) was used to conceal treatment allocation. Enrolment was done by study centre staff who were not involved in the running of the clinical trial or in data collection.

Procedures

Patients received belantamab mafodotin 2·5 mg/kg or 3·4 mg/kg (frozen solution) every 3 weeks intravenously over 30 min or longer on day 1 of each cycle, until disease progression or unacceptable toxicity. Dose modifications, including delays or reductions, were permitted for toxicity, and dosing delays for toxicity or for medical or surgical and logistical reasons not related to treatment. Criteria for dose reductions, dose delays, and withdrawal of patients from the study are available in the study protocol. Laboratory assessments for haematology, clinical chemistry, and urinalysis were done at screening, on day 1 during cycle 1, and every 3 weeks thereafter. Radiography for skeletal lytic lesions (method per institutional guidance) was done at screening and as clinically indicated for patients without extramedullary disease (patients with extramedullary disease received more frequent assessments, as defined in the protocol). Adverse events were monitored throughout the study until 45 days after study discontinuation and coded according to the Medical Dictionary for Regulatory Activities, version 22. All adverse events were graded by Common Terminology Criteria for Adverse Events criteria, version 4.03.[14]

Baseline and subsequent ophthalmic examinations were done pre-dose and every 3 weeks by an ophthalmologist (or an optometrist if an ophthalmologist was not available). Corticosteroid eye drops and preservative-free artificial tears were used in both eyes to mitigate corneal events, a known toxic effect of MMAF and commonly reported in DREAMM-1.[12,13,15] In an ocular substudy (approximately 15 patients per dose cohort), corticosteroid eye drops were applied to only one eye to evaluate the effect of corticosteroid eye drops on keratopathy (changes to the corneal epithelium observed by ophthalmic examination) and patient-reported corneal-related symptoms. At the start of infusion, cooling eye masks could be applied (appendix pp 5–6).

Outcomes

The primary outcome was the proportion of patients achieving an overall response as assessed by an independent review committee, defined as the percentage of patients with confirmed partial response or better (in accordance with the International Myeloma Working Group uniform response criteria for multiple myeloma[16]) when assessed every 3 weeks after cycle 1. Key secondary outcomes included duration of response (onset of response to disease progression), time to response (randomisation to response), progression-free survival (randomisation to disease progression or death), overall survival (randomisation to death), proportion of patients achieving clinical benefit (minimal response or better),[16] and safety (adverse events, serious adverse events, and adverse events of special interest, which included thrombocytopenia, infusion-related reactions, and keratopathy). In the protocol prespecified ocular substudy, the time to development of keratopathy and symptoms was evaluated for the eye receiving corticosteroid eye drops compared with the eye not receiving this treatment.

The investigator-assessed proportion of patients achieving an overall response (a secondary outcome) and other secondary outcomes of time to response (from randomisation to first documented evidence of response), time to progression (from randomisation to disease progression), anti-drug antibodies (incidence and titres), pharmacokinetics (plasma concentrations of belantamab mafodotin analytes), patient-reported outcomes, and health-related quality-of-life outcomes will be reported separately.

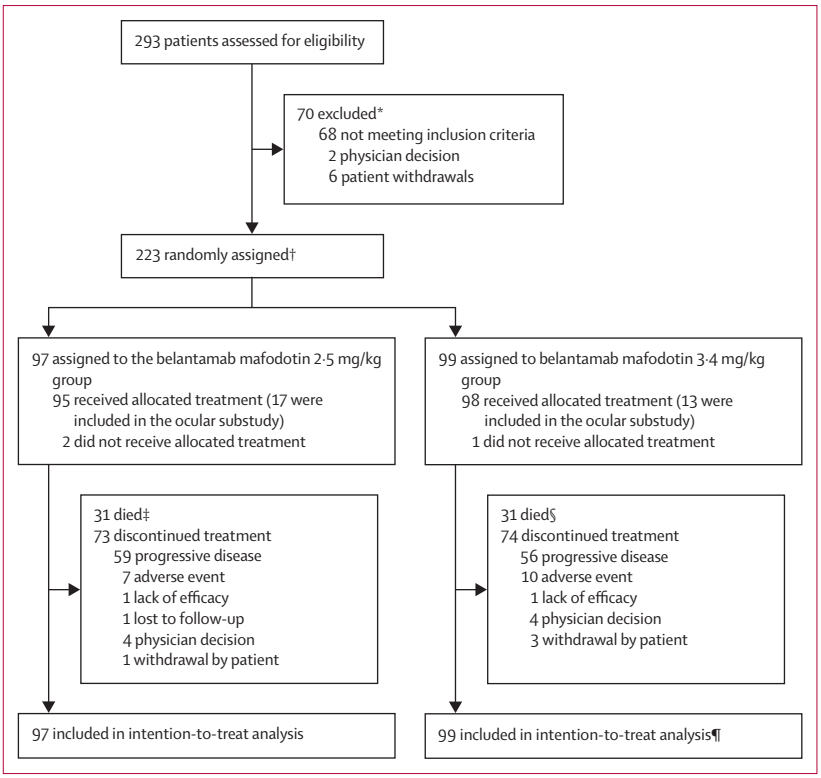


Figure 1: **Trial profile**

*Patients could have more than one reason for failure. †Two patients were randomly assigned again and counted twice (once per each randomisation), and an additional independent cohort of 25 patients was recruited and received a lyophilised configuration of belantamab mafodotin 3·4 mg/kg and underwent the same assessments and procedures as the main study; this cohort will be analysed separately from patients randomised to the frozen solution, the results of which will be reported elsewhere. ‡Causes of death were disease under study (n=25), adverse event potentially related to treatment (n=1, sepsis), other (n=2, myocardial infarction), or unknown cause (n=3). An additional patient randomly assigned to the 2·5 mg/kg cohort, but who did not receive study treatment, died (cause of death: disease under study). §Causes of death were disease under study (n=23), adverse event potentially related to treatment (n=1, haemophagocytic lymphohistiocytosis in the background of bacterial or viral infection), other (n=7; one case each of brain herniation, cardiac insufficiency, haemorrhage, respiratory infection, heart failure, sepsis, and cancer). ¶One patient randomised to the 3·4 mg/kg lyophilised configuration received the 3·4 mg/kg frozen configuration as a first dose, and never received the lyophilised configuration during the study, and therefore was included in the 3·4 mg/kg frozen arm for the safety population.

Statistical analysis

DREAMM-2 was a two-arm study (ie, the two treatment groups were not compared). The sample size calculation was based on a response rate of 30% or greater in each of the two belantamab mafodotin treatment arms (2·5 mg/kg or 3·4 mg/kg) compared with the historical control (≤15%). Statistical power scenarios are detailed in the protocol. The planned sample size was 65 participants in each of the two dose arms.

The intention-to-treat population comprised all randomly assigned patients, regardless of treatment administration. All patients who received at least one dose of belantamab mafodotin were included in the safety population. All patients who received two or more doses of belantamab mafodotin and completed at least one disease assessment after the second dose were considered evaluable for response. This analysis was done 6 months after the last participant was enrolled to allow sufficient data maturity of all drug activity endpoints. An interim analysis for the primary outcomes (the first 51 evaluable patients) and a sensitivity analysis of the primary and selected secondary outcomes (the first 130 randomised patients) were done (data not shown).

When calculating the proportion of patients achieving an overall response, patients with unknown or missing response data were treated as non-responders. For the primary analysis, two-sided 97·5% exact CIs are reported, in line with the study protocol. No hypothesis testing was done in the prespecified analysis of the proportion of patients achieving an overall response according to the subcohorts of age, sex, ethnicity, International Staging System (ISS) stage at screening, baseline renal impairment, previous anticancer therapy, type of myeloma, cytogenetic risk, extramedullary disease, number of lines of previous therapy, and drugs that patients were refractory to. Progression-free survival, duration of response, and time to response were analysed with the Kaplan–Meier method. The non-binding futility boundary was determined to ensure good operating characteristics, then a two-step approach was taken to determine the futility stopping rule. Descriptive statistics were used for pre-treatment characteristics and adverse events (appendix p 7).

We analysed duration of response, overall survival, and progression-free survival according to response in a post-hoc analysis.

This study was overseen by an independent data monitoring committee. The sample size calculation was done with East software (version 6.4). Analyses were done with SAS (version 9.4).

This study is registered with ClinicalTrials.gov, NCT03525678, and is ongoing.

Role of the funding source

The sponsor was involved in study design and implementation, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to the data upon request and had final responsibility for the decision to submit for publication.

Results

Between June 18, 2018, and Jan 2, 2019, 293 patients were screened. 221 patients were randomly assigned, of whom 196 were randomly assigned to the 2·5 mg/kg (n=97) and 3·4 mg/kg (n=99) cohorts and included in the intention-to-treat population. 30 of these patients were included in the ocular substudy (17 in the 2·5 mg/kg cohort and 13 in the 3·4 mg/kg cohort; figure 1). In the safety population (95 patients in the 2·5 mg/kg cohort and 99 in the 3·4 mg/kg cohort), as of the data cutoff date of June 21, 2019, 47 patients (22 [23%] of 95 in the 2·5 mg/kg cohort and 25 [25%] of 99 in the 3·4 mg/kg cohort) were still receiving study treatment. Patients in both cohorts received a median of three treatment cycles (range 1–11 in the 2·5 mg/kg cohort and 1–10 in the 3·4 mg/kg cohort).

	Belantamab mafodotin 2·5 mg/kg group (n=97)	Belantamab mafodotin 3·4 mg/kg group (n=99)
Age, median (IQR), years	65 (60–70)	67 (61–72)
18 to <65 years	45 (46%)	36 (36%)
65 to <75 years	39 (40%)	46 (46%)
≥75 years	13 (13%)	17 (17%)
Sex		
Male	51 (53%)	56 (57%)
Female	46 (47%)	43 (43%)
Race		
White or White European	72 (74%)	83 (84%)
Black or African-American	16 (16%)	11 (11%)
Renal impairment per eGFR (mL/min per 1·73m²)		
Normal (≥90)	19 (20%)	17 (17%)
Mild (≥60 to <90)	48 (49%)	52 (52%)
Moderate (≥30 to <60)	24 (25%)	22 (22%)
Severe (≥15 to <30)	2 (2%)	5 (5%)
Time from initial diagnosis, median (IQR), years*	5·49 (4·01–7·02)	5·08 (4·16–7·48)
ISS disease stage at screening		
Stage I	21 (22%)	18 (18%)
Stage II	33 (34%)	51 (52%)
Stage III	42 (43%)	30 (30%)
Unknown	1 (1%)	0
Cytogenetic abnormalities		
t(11;14)	16 (16%)	9 (9%)
t(14;20)	3 (3%)	0
Del 13	18 (19%)	17 (17%)
Hyperdiploidy	7 (7%)	4 (4%)
Other	28 (29%)	23 (23%)
High-risk cytogenetics	41 (42%)	47 (47%)
17p13del	16 (16%)	22 (22%)
t(4;14)	11 (11%)	11 (11%)
t(14;16)	7 (7%)	2 (2%)
1q21+	25 (26%)	30 (30%)
Type of myeloma		
IgG	65 (67%)	73 (74%)
Non-IgG or unknown	32 (33%)	26 (26%)
Extramedullary disease	22 (23%)	18 (18%)
Previous lines of therapy†		
Median (range)	7 (3–21)	6 (3–21)
≤4 lines	16 (16%)	17 (17%)
>4 lines	81 (84%)	82 (83%)
(Continued from previous column)		
Previous therapies received		
Proteasome inhibitor		
Bortezomib	95 (98%)	97 (98%)
Carfilzomib	74 (76%)	64 (65%)
Immunomodulatory drug		
Lenalidomide	97 (100%)	99 (100%)
Pomalidomide	89 (92%)	84 (85%)
Anti-CD38 monoclonal antibody		
Daratumumab	97 (100%)	96 (97%)
Isatuximab	3 (3%)	2 (2%)
Refractory to previous therapies‡		
Proteasome inhibitor		
Bortezomib	74 (76%)	74 (75%)
Carfilzomib	63 (65%)	57 (58%)
Immunomodulatory drug		
Lenalidomide	87 (90%)	88 (89%)
Pomalidomide	84 (87%)	77 (78%)
Anti-CD38 monoclonal antibody		
Daratumumab	97 (100%)	91 (92%)
Isatuximab	3 (3%)	1 (1%)

Data are n (%) unless otherwise specified. eGFR=estimated glomerular filtration rate. ISS=International Staging System. *Data available for 47 patients in the 2·5 mg/kg cohort and 36 patients in the 3·4-mg/kg cohort. †The number of previous lines of therapy is derived as the number of previous anticancer regimens received by a patient as reported on the electronic case report form. Combination therapy containing multiple components was counted as one regimen. ‡Based on data available at the time of database lock; however, all patients were refractory to a proteasome inhibitor, immunomodulatory drug, and an anti-CD38 monoclonal antibody as per eligibility criteria.

Table 1: **Demographics and baseline disease and clinical characteristics in the intention-to-treat population**

Baseline characteristics are presented in table 1. Patients with ISS stage III disease, extramedullary disease, and high-risk cytogenetic features were well represented in both cohorts. As per the inclusion criteria, all participants were refractory to immunomodulatory drugs and proteasome inhibitors, and had previously received an anti-CD38 monoclonal antibody (upon analysis all patients were refractory to anti-CD38 monoclonal antibodies). 33 (34%) patients received an anti-CD38 monoclonal antibody as the last previous anticancer therapy in the 2·5 mg/kg cohort, as did 37 (37%) patients in the 3·4 mg/kg cohort.

30 (31%; 97·5% CI 20·8–42·6) of 97 patients in the 2·5 mg/kg cohort and 34 (34%; 23·9–46·0) of 99 patients in the 3·4 mg/kg cohort achieved an overall response as assessed by the independent review committee (figure 2). A very good partial response or better was achieved by 18 (19%) of 97 patients in the 2·5 mg/kg cohort (18 [60%] of 30 responders) and by 20 (20%) of 99 patients in the 3·4 mg/kg cohort (20 [59%] of 34 responders), which included stringent complete or complete responses in three patients in each cohort. The overall proportions of patients achieving a response in patient subcohorts are shown in figure 3. 33 (34%; 95% CI 24·7–44·3) of 97 patients in the 2·5 mg/kg cohort and 39 (39%; 29·7–49·7) of 99 in the 3·4 mg/kg cohort achieved a clinical benefit (minimal response or better as assessed by the independent review committee).

At the median duration of follow-up (6·3 months [IQR 3·7–7·7] in the 2·5 mg/kg cohort and 6·9 months [4·8–7·9] in the 3·4 mg/kg cohort), the median duration of response was not reached (appendix p 8). Based on the Kaplan–Meier curve (appendix p 8), the probability of having a duration of response of 4 months or longer was estimated to be 78% (95% CI 57–89) in the 2·5 mg/kg cohort and 87% (69–95) in the 3·4 mg/kg cohort. At the data cutoff date (June 21, 2019), 18 patients in 2·5 mg/kg group and 25 in the 3·4 mg/kg group had a duration of response of 4 months or longer with progression-free survival follow-up ongoing and continued to be on treatment. At the time of data cutoff, the overall survival data were not mature (figure 4A, C); 32 (33%) of 97 patients in 2·5 mg/kg cohort and 31 (31%) of 99 in the 3·4 mg/kg cohort died. Median progression-free survival was 2·9 months (95% CI 2·1–3·7) in the 2·5 mg/kg cohort and 4·9 months (2·3–6·2) in the 3·4 mg/kg cohort (figure 4B, D). At the time of data cutoff, 56 (58%) patients in 2·5 mg/kg cohort and 55 (56%) in the 3·4 mg/kg cohort had disease progression or died. Post-hoc analyses of duration of response, overall survival, and progression-free survival by response are shown in the appendix (p 8).

Overall, 93 (98%) of 95 patients in the 2·5 mg/kg cohort and 99 (100%) of 99 in the 3·4 mg/kg cohort had at least one adverse event. The median dose intensity was 2·47 mg/kg (IQR 1·56–2·50) for the 2·5 mg/kg group. However, because of the higher incidence of dose modifications, the dose intensity was lower than the intended dose for the 3·4 mg/kg dose group (median 2·95 mg/kg; IQR 1·85–3·40). Adverse events leading to dose delays were reported in 51 (54%) of 95 patients in the 2·5 mg/kg cohort and in 61 (62%) of 99 patients in the 3·4 mg/kg cohort. Adverse events leading to dose reductions were reported in 28 (29%) of 95 patients and 41 (41%) of 99 patients. In the 2·5 mg/kg cohort, 28 (29%) of 95 patients had a single permitted dose reduction to 1·92 mg/kg, whereas 28 (28%) of 99 patients in the 3·4 mg/kg cohort had a permitted dose reduction to 2·5 mg/kg, and 14 (14%) of 99 had two permitted dose reductions (to 2·5 mg/kg and subsequently to 1·92 mg/kg). Eight (8%) of 95 patients in the 2·5 mg/kg cohort and ten (10%) of 99 patients in the 3·4 mg/kg cohort had adverse events leading to permanent treatment discontinuation, and keratopathy was the most common reason for treatment discontinuation (in one [12·5%] of eight patients in the 2·5 mg/kg cohort and in three [30%] of ten patients in the 3·4 mg/kg

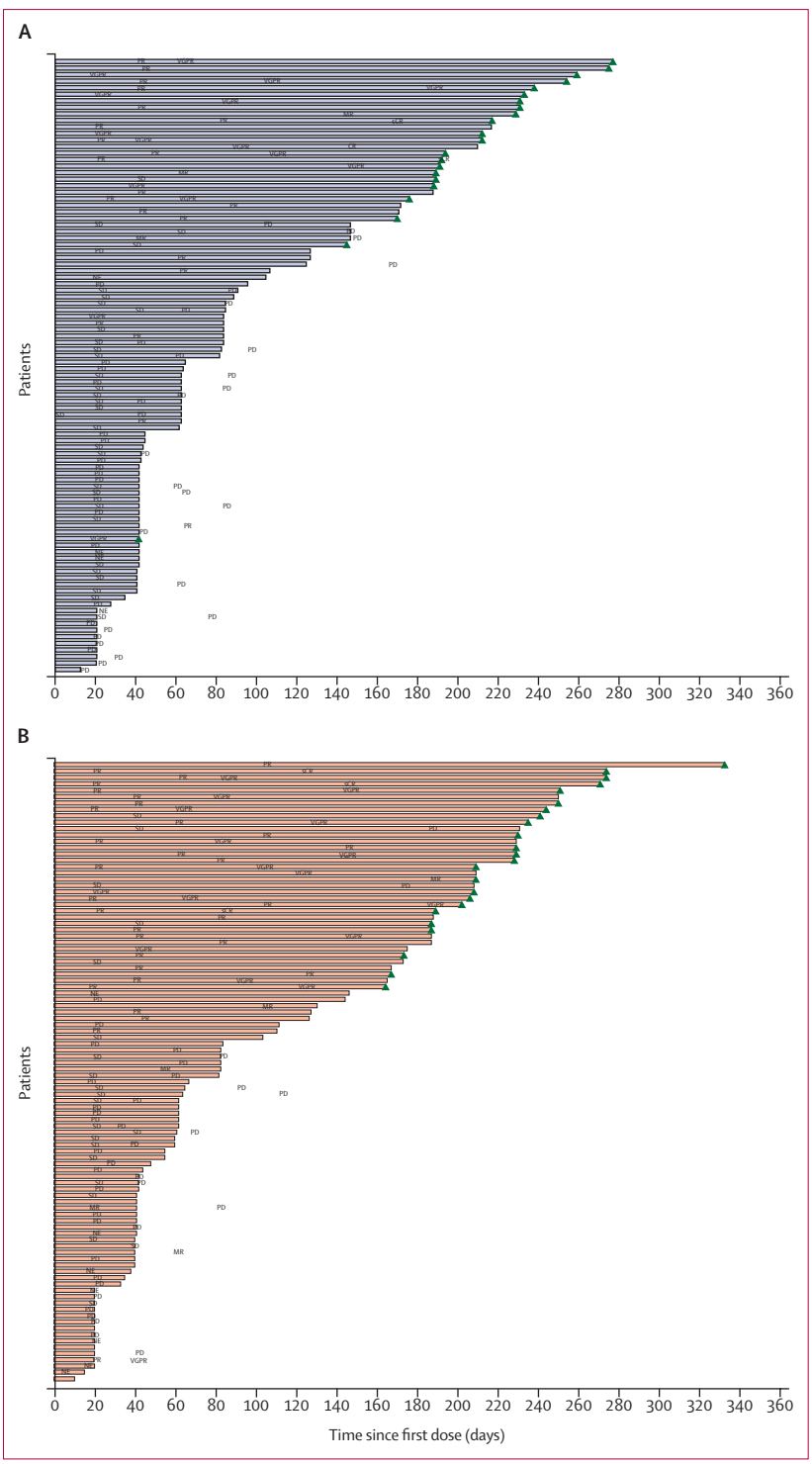
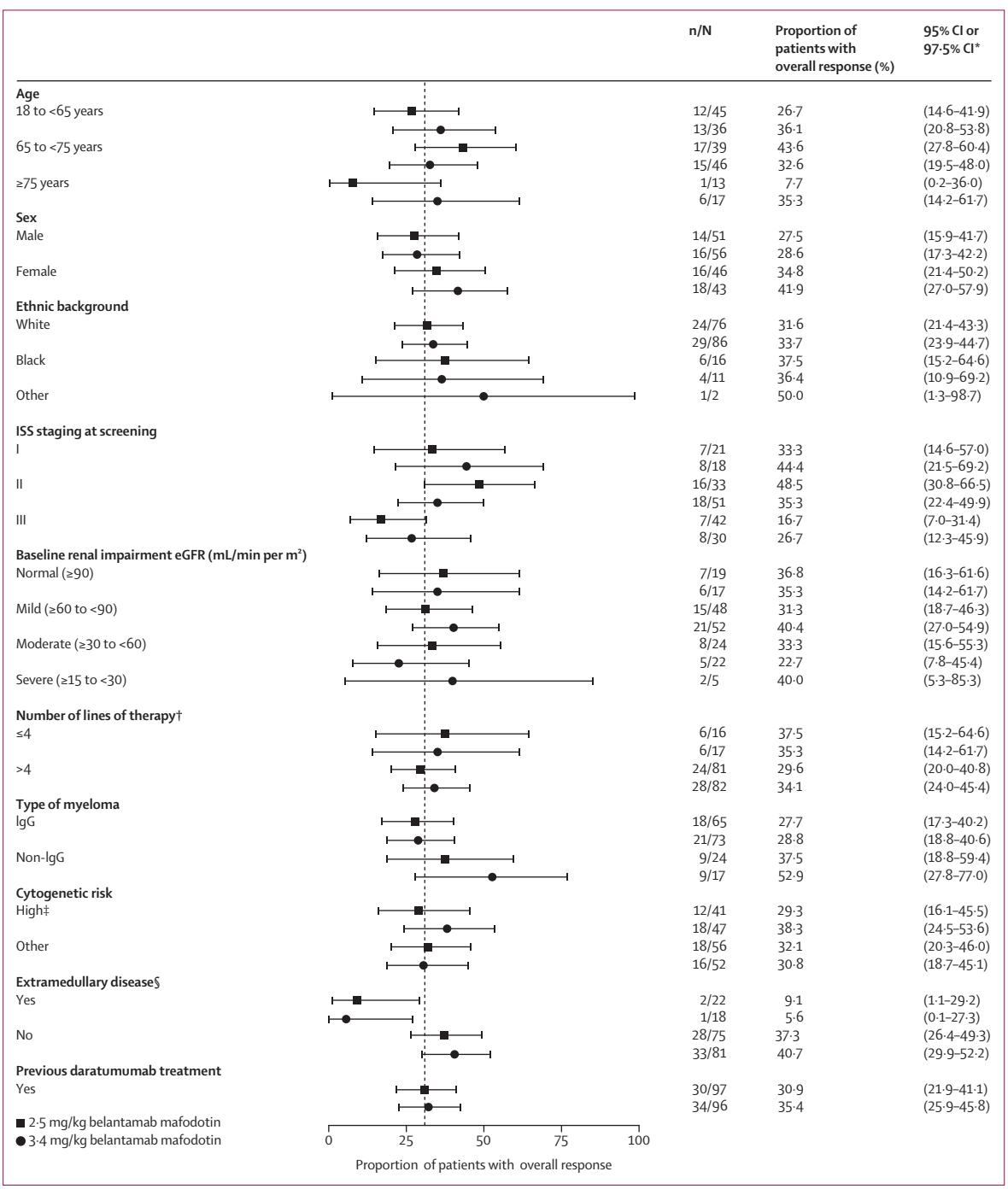


Figure 2: **Time from first dose to best confirmed response in the 2·5 mg/kg cohort (A) and the 3·4 mg/kg cohort (B)**
Responses were assessed in the intention-to-treat population (including all patients randomly assigned) by an independent review committee according to the International Myeloma Working Cohort Uniform Criteria Consensus Recommendations.[16] Green triangles represent patients with study treatment ongoing. Responses are indicated at the time of the first report of a partial response or better, followed by best response, unless the two occurred concurrently. One patient in the 2·5 mg/kg cohort did not have any response assessments completed. The best confirmed response for this patient was derived as not estimable but could not be included on the plot as no date was associated with the non-estimable response. CR=complete response. MR=minimal response. NE=not evaluable. PD=progressive disease. PR=partial response. sCR=stringent complete response. SD=stable disease. VGPR=very good partial response.

cohort). The most common grade 1–2 adverse event was keratopathy, and the most common grade 3–4 adverse events in the safety population were keratopathy (in 26 [27%] of 95 patients in the 2·5 mg/kg cohort and 21 [21%] of 99 patients in the 3·4 mg/kg cohort), thrombocytopenia (in 19 [20%] of 95 and 33 [33%] of 99), and anaemia (in 19 [20%] of 95 and 25 [25%] of 99; table 2). The frequency of grade 3 or worse pneumonia (in four [4%] of 95 patients in the 2·5 mg/kg cohort and 11 [11%] of 99 patients in the 3·4 mg/kg cohort) and upper respiratory tract infections (one [1%] of 99 patients in the 3·4 mg/kg cohort) was low (table 2). Serious adverse events were reported in 38 (40%) of 95 patients in the 2·5 mg/kg cohort and in 47 (47%) of 99 patients in the 3·4 mg/kg cohort (appendix pp 10–11). Three (3%) of 95 patients in the 2·5 mg/kg cohort and seven (7%) of



(Figure 3 continues on next page)

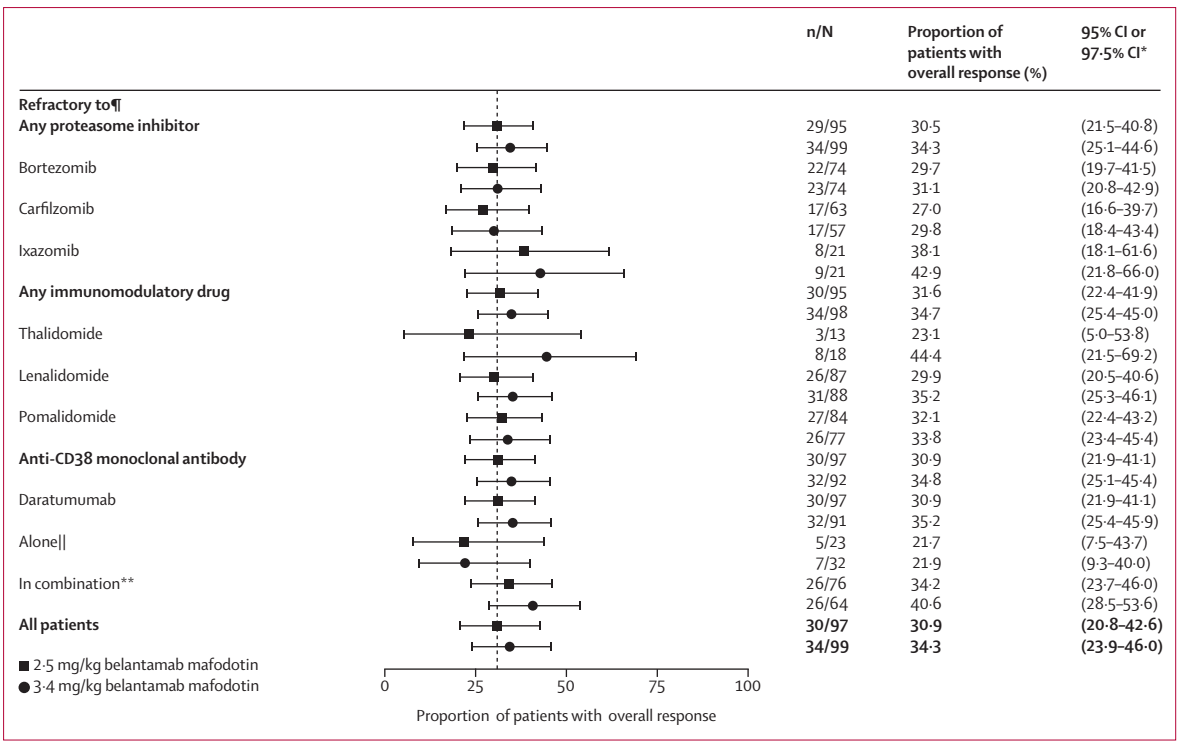


Figure 3: **Overall proportion of patients achieving a response by dose and subcohort in the intention-to-treat population**
The confidence interval is based on the Exact method. No responders in the following categories for the 2·5 mg/kg group: ethnic background other (zero of five patients), International Staging System stage unknown at screening (zero of one), severe baseline renal impairment (≥15 to <30; zero of two), refractory to isatuximab (zero of three); and in the following categories for the 3·4 mg/kg group: previous daratumumab treatment (zero of three) and refractory to isatuximab (zero of one).*97·5% CIs reported for "all patients" as per the study protocol; in all other instances, 95% CIs are reported. Responses were assessed in the intention-to-treat population (including all randomised patients) by an independent review committee according to the International Myeloma Working Cohort Uniform Criteria Consensus Recommendations.[16] †The number of previous lines of therapy was derived as the number of previous anticancer regimens received by a patient as reported on the electronic case report form. Combination therapies containing multiple components were counted as one regimen. ‡A patient is considered as high risk if they have any of the following cytogenetics: t(4:14), t(14:16), 17p13del, or 1q21+. §Post-hoc analysis. ¶Based on data available at the time of database lock; however, all patients were refractory to a proteasome inhibitor, immunomodulatory drug, and an anti-CD38 monoclonal antibody as per eligibility criteria. ||Defined as previous regimen with daratumumab monotherapy. **Defined as previous regimen with daratumumab in combination with other drugs.

99 patients in the 3·4 mg/kg cohort died because of a serious adverse event. Two deaths were considered potentially related to study treatment by the investigator: one case of sepsis (in the 2·5 mg/kg cohort) and one case of haemophagocytic lymphohistiocytosis (in the background of bacterial or viral infection in the 3·4 mg/kg cohort).

Adverse events of special interest (thrombocytopenia, infusion-related reactions, and keratopathy) are summarised in the appendix (p 11). Grade 2 or worse bleeding events occurred in five (5%) of 95 patients in the 2·5 mg/kg cohort and 17 (17%) of 99 patients in the 3·4 mg/kg cohort and any grade neutropenia occurred in 13 (14%) of 95 patients in the 2·5 mg/kg cohort and 27 (27%) of 99 patients in the 3·4 mg/kg cohort. Among patients with infusion-related reactions, events were predominantly grade 1–2 (in 17 [18%] of 95 patients in the 2·5 mg/kg cohort and 15 [15%] of 99 patients in the 3·4 mg/kg cohort) and occurred with the first infusion (in 18 [19%] of 95 and 14 [14%] of 99 patients). Few patients had more than one infusion-related reaction (eight [8%] of 95 and seven [7%] of 99 patients). One patient (in the 2·5 mg/kg cohort) discontinued treatment because of infusion-related reactions (grade 3 infusion-related reactions at first and second infusion). Although not mandated in the protocol, premedications for infusion-related reactions prophylaxis were administered to 30 [32%] of 95 patients in the 2·5 mg/kg cohort and to 39 [39%] of 99 patients in the 3·4 mg/kg cohort. Of those who received prophylaxis for infusion-related reactions before cycle 1, eight (36%) of 22 patients in the 2·5 mg/kg group and six (22%) of 27 patients in the 3·4 mg/kg group had infusion-related reactions.

Keratopathy (ie, corneal epithelium changes observed by ophthalmic examination) was reported in both cohorts (table 2). Although rare, these events were the most common adverse events leading to permanent treatment discontinuation (in one [1%] of 95 patients and three [3%] of 99 patients) or, more commonly, dose reductions (in 22 [23%] of 95 patients and 27 [27%] of 99 patients) and delays (in 45 [47%] of 95 patients and 48 [48%] of 99 patients). Dose delays for keratopathy started at week 4 in both cohorts, whereas dose reductions started later in the 2·5 mg/kg cohort than in the 3·4 mg/kg cohort

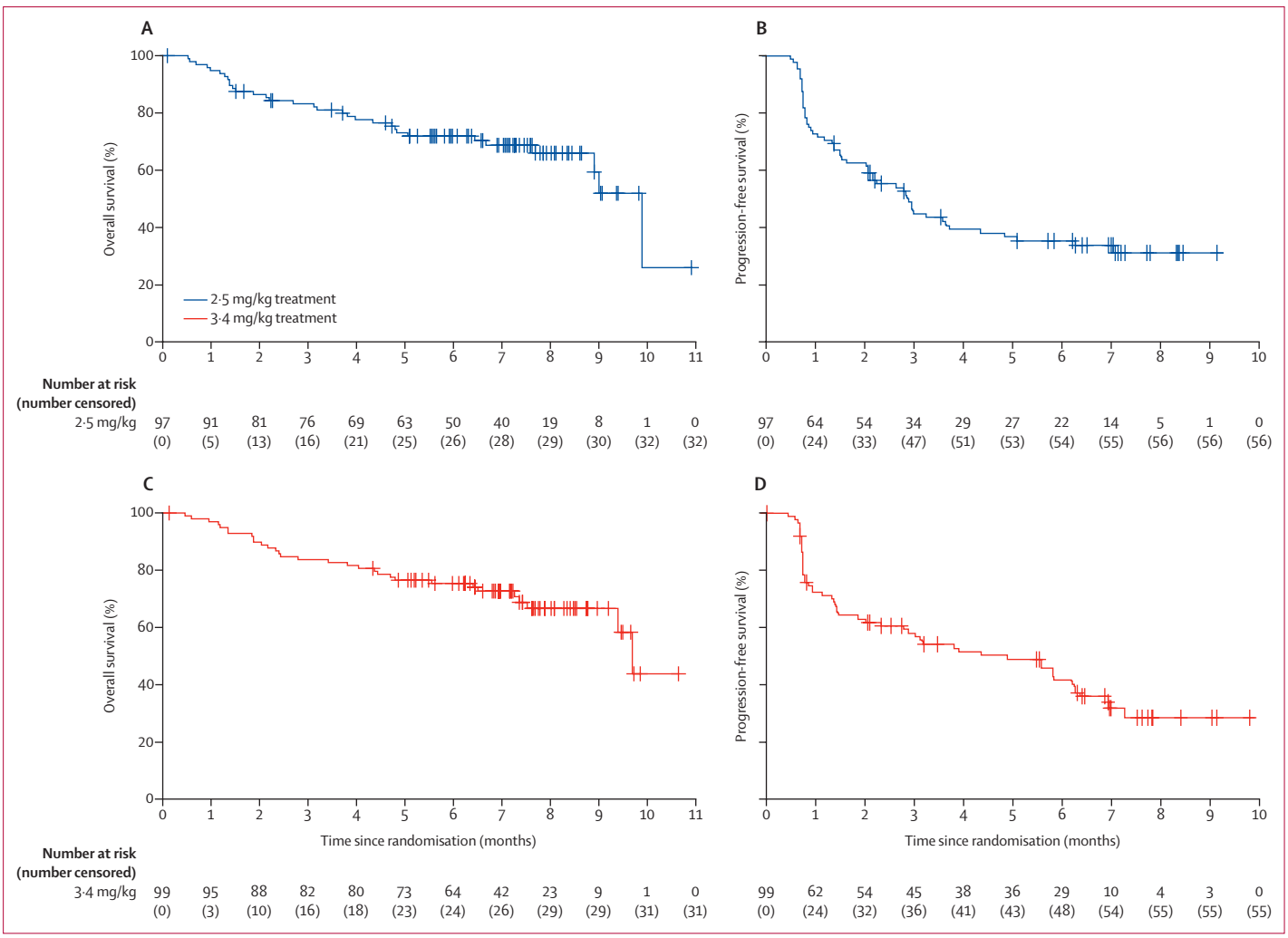


Figure 4: **Overall survival in the 2·5 mg/kg cohort (A), progression-free survival in the 2·5 mg/kg cohort (B), overall survival in the 3·4 mg/kg cohort (C), and progression-free survival in the 3·4 mg/kg cohort (D)***

*Responses were assessed in the intention-to-treat population (including all randomly assigned patients) by an independent review committee according to the International Myeloma Working Cohort Uniform Criteria Consensus Recommendations.[16]

(at week 13 *vs* week 4). Most patients in both cohorts with treatment delays due to keratopathy (45 patients in the 2·5 mg/kg cohort and 51 in the 3·4 mg/kg cohort) re-initiated treatment (31 [69%] of 45 and 39 [76%] of 51 patients), with median time to treatment re-initiation of 83 days (range 28–146) in the 2·5 mg/kg cohort and 63 days (21–147) in the 3·4 mg/kg cohort. Four patients (one in the 2·5 mg/kg cohort and three in the 3·4 mg/kg cohort) permanently discontinued treatment because of keratopathy; only one of these patients also reported corneal symptoms (dry eye or blurred vision). Although follow-up of patients was limited, among those with keratopathy worse than baseline at the end of treatment, the events resolved in nine (36%) of 25 patients in the 2·5 mg/kg cohort, with a median time to resolution of 71 days (IQR 57–99), and in eight (28%) of 29 patients in the 3·4 mg/kg cohort, with a median time to resolution of 96 days (70–127). The change in cornea is primarily limited to the epithelium with less than 10% of patients with normal corneal stroma or endothelium at baseline developing an abnormal finding in their worst eye. The most common patient-reported corneal symptoms were blurred vision and dry eye (appendix p 9). Two patients (one in each cohort) had dry eye or blurred vision without accompanying keratopathy. One (1%) patient in the 2·5 mg/kg cohort and two (2%) patients in the 3·4 mg/kg cohort had a transient worsening of their vision (worse than or equal to 20/200) in both eyes; however, all three patients saw an improvement in best-corrected visual acuity (ie, returned to baseline during follow-up) and keratopathy resolution. Based on limited follow-up data, vision returned to baseline or near baseline in most cases (35 [85%] of 41 patients recovered from their first occurrence in the 2·5 mg/kg group as did

	Belantamab mafodotin 2·5 mg/kg group (n=95)				Belantamab mafodotin 3·4 mg/kg group (n=99)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Keratopathy or changes to corneal epithelium*	41 (43%)	26 (27%)	0	0	53 (54%)	20 (20%)	1 (1%)	0
Thrombocytopaenia†	14 (15%)	8 (8%)	11 (12%)	0	24 (24%)	11 (11%)	22 (22%)	1 (1%)
Anaemia	4 (4%)	19 (20%)	0	0	12 (12%)	22 (22%)	3 (3%)	0
Nausea‡	23 (24%)	0	0	0	31 (31%)	1 (1%)	0	0
Pyrexia‡	18 (19%)	2 (2%)	1 (1%)	0	21 (21%)	4 (4%)	0	0
Blurred vision§	17 (18%)	4 (4%)	0	0	28 (28%)	2 (2%)	0	0
Infusion-related reactions¶	17 (18%)	3 (3%)	0	0	15 (15%)	1 (1%)	0	0
Increased aspartate aminotransferase	17 (18%)	2 (2%)	0	0	18 (18%)	6 (6%)	0	0
Fatigue‡	13 (14%)	2 (2%)	0	0	21 (21%)	5 (5%)	0	0
Dry eye‖	12 (13%)	1 (1%)	0	0	23 (23%)	0	0	0
Neutropenia**	4 (4%)	5 (5%)	4 (4%)	0	12 (12%)	12 (12%)	3 (3%)	0
Hypercalcaemia	6 (6%)	4 (4%)	3 (3%)	0	13 (13%)	3 (3%)	0	0
Decreased lymphocyte count	1 (1%)	8 (8%)	4 (4%)	0	4 (4%)	6 (6%)	2 (2%)	0
Diarrhoea‡	11 (12%)	1 (1%)	0	0	14 (14%)	1 (1%)	0	0
Constipation	12 (13%)	0	0	0	9 (9%)	0	0	0
Decreased appetite	11 (12%)	0	0	0	16 (16%)	2 (2%)	0	0
Arthralgia	10 (11%)	1 (1%)	0	0	7 (7%)	0	0	0
Increased blood creatinine	7 (7%)	3 (3%)	0	0	10 (10%)	1 (1%)	0	0
Back pain	8 (8%)	2 (2%)	0	0	9 (9%)	2 (2%)	0	0
Headache	9 (9%)	0	0	0	13 (13%)	1 (1%)	0	0
Hyperuricaemia	6 (6%)	0	3 (3%)	0	5 (5%)	0	3 (3%)	0
Leucopenia	5 (5%)	3 (3%)	1 (1%)	0	5 (5%)	2 (2%)	0	0
Increased gamma-glutamyltransferase	5 (5%)	3 (3%)	0	0	5 (5%)	8 (8%)	0	0
Increased blood alkaline phosphatase	7 (7%)	1 (1%)	0	0	12 (12%)	0	0	0
Vomiting‡	5 (5%)	2 (2%)	0	0	20 (20%)	0	0	0
Cough‡	7 (7%)	0	0	0	19 (19%)	0	0	0
Epistaxis	6 (6%)	1 (1%)	0	0	17 (17%)	2 (2%)	0	0
Upper respiratory tract infection	7 (7%)	0	0	0	16 (16%)	1 (1%)	0	0
Hypokalaemia	5 (5%)	0	2 (2%)	0	11 (11%)	2 (2%)	0	0
Decreased white blood cell count	5 (5%)	1 (1%)	1 (1%)	0	7 (7%)	2 (2%)	1 (1%)	0
Hypertension‡	5 (5%)	1 (1%)	1 (1%)	0	3 (3%)	5 (5%)	1 (1%)	0
Hypophosphataemia	2 (2%)	4 (4%)	1 (1%)	0	3 (3%)	3 (3%)	1 (1%)	0
Hypomagnesaemia	6 (6%)	0	0	0	5 (5%)	1 (1%)	0	0
Dyspnoea	4 (4%)	1 (1%)	1 (1%)	0	5 (5%)	0	0	0
Lymphopenia	2 (2%)	4 (4%)	0	0	2 (2%)	2 (2%)	1 (1%)	0
Acute kidney injury	4 (4%)	2 (2%)	0	0	2 (2%)	0	1 (1%)	0
Pain in extremity	5 (5%)	0	0	0	11 (11%)	1 (1%)	0	0
Hyponatraemia	3 (3%)	2 (2%)	0	0	7 (7%)	4 (4%)	0	0
Hypoalbuminaemia	4 (4%)	1 (1%)	0	0	6 (6%)	4 (4%)	0	0
Lung infection	2 (2%)	2 (2%)	0	1 (1%)	3 (3%)	2 (2%)	0	0
Pain	4 (4%)	1 (1%)	0	0	5 (5%)	0	0	0
Increased blood creatine phosphokinase	4 (4%)	0	1 (1%)	0	3 (3%)	0	0	0
Pneumonia	0	3 (3%)	1 (1%)	0	2 (2%)	9 (9%)	0	2 (2%)
Asthenia	4 (4%)	0	0	0	8 (8%)	2 (2%)	0	0
Bone pain	1 (1%)	3 (3%)	0	0	8 (8%)	1 (1%)	0	0
Increased blood lactate dehydrogenase	4 (4%)	0	0	0	6 (6%)	1 (1%)	0	0
Hypocalcaemia	3 (3%)	1 (1%)	0	0	3 (3%)	0	0	0
Proteinuria	4 (4%)	0	0	0	2 (2%)	1 (1%)	0	0
Hyperglycaemia	2 (2%)	1 (1%)	0	0	5 (5%)	1 (1%)	0	0

(Table 2 continues on next page)

	Belantamab mafodotin 2·5 mg/kg group (n=95)				Belantamab mafodotin 3·4 mg/kg group (n=99)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Muscular weakness	2 (2%)	1 (1%)	0	0	4 (4%)	0	0	0
Pleural effusion	2 (2%)	1 (1%)	0	0	2 (2%)	1 (1%)	0	0
Vascular device infection	2 (2%)	1 (1%)	0	0	1 (1%)	0	0	0
Staphylococcal sepsis	1 (1%)	1 (1%)	1 (1%)	0	0	0	0	0
Increased C-reactive protein	2 (2%)	0	0	0	4 (4%)	1 (1%)	0	0
Sepsis	0	0	1 (1%)	1 (1%)	0	2 (2%)	1 (1%)	0
Chest pain	1 (1%)	0	1 (1%)	0	1 (1%)	1 (1%)	0	0
Delirium	1 (1%)	1 (1%)	0	0	0	2 (2%)	0	0
Hypermagnesaemia	0	2 (2%)	0	0	2 (2%)	0	0	0
Stomatitis	1 (1%)	1 (1%)	0	0	2 (2%)	0	0	0
Gastrointestinal haemorrhage	2 (2%)	0	0	0	0	1 (1%)	0	0
Cellulitis	1 (1%)	1 (1%)	0	0	0	1 (1%)	0	0
Device-related infection	1 (1%)	0	1 (1%)	0	0	0	0	0
Confusional state	1 (1%)	0	0	0	2 (2%)	2 (2%)	0	0
Sinusitis	1 (1%)	0	0	0	3 (3%)	1 (1%)	0	0
Atelectasis	1 (1%)	0	0	0	2 (2%)	1 (1%)	0	0
Gingival bleeding	1 (1%)	0	0	0	1 (1%)	2 (2%)	0	0
Staphylococcal infection	1 (1%)	0	0	0	2 (2%)	1 (1%)	0	0
Paraesthesia	0	1 (1%)	0	0	3 (3%)	0	0	0
General physical health deterioration	1 (1%)	0	0	0	1 (1%)	1 (1%)	0	0
Lethargy	0	1 (1%)	0	0	2 (2%)	0	0	0
Cardiac arrest	0	0	0	1 (1%)	0	0	0	1 (1%)
Renal failure	0	1 (1%)	0	0	1 (1%)	0	0	0
Renal impairment	0	1 (1%)	0	0	1 (1%)	0	0	0
Spinal compression fracture	0	1 (1%)	0	0	0	1 (1%)	0	0
Staphylococcal bacteraemia	0	1 (1%)	0	0	0	1 (1%)	0	0
Viral infection	1 (1%)	0	0	0	0	0	0	1 (1%)
Ascites	0	1 (1%)	0	0	0	0	0	0
Electrocardiogram T wave inversion	0	1 (1%)	0	0	0	0	0	0
Enterocolitis	0	1 (1%)	0	0	0	0	0	0
Exophthalmos	0	1 (1%)	0	0	0	0	0	0
Abnormal gamma-glutamyltransferase	0	1 (1%)	0	0	0	0	0	0
Glaucoma	0	1 (1%)	0	0	0	0	0	0
Herpes simplex pneumonia	0	1 (1%)	0	0	0	0	0	0
Humerus fracture	0	1 (1%)	0	0	0	0	0	0
Mitral valve disease	0	1 (1%)	0	0	0	0	0	0
Posterior reversible encephalopathy syndrome	0	1 (1%)	0	0	0	0	0	0
Respiratory failure	0	1 (1%)	0	0	0	0	0	0
Seizure	0	1 (1%)	0	0	0	0	0	0
Tibia fracture	0	1 (1%)	0	0	0	0	0	0
Decreased urine output	0	0	1 (1%)	0	0	0	0	0
Vaginitis gardnerella	0	1 (1%)	0	0	0	0	0	0
Dizziness	0	0	0	0	5 (5%)	1 (1%)	0	0
Haematoma	0	0	0	0	3 (3%)	2 (2%)	0	0
Escherichia urinary tract infection	0	0	0	0	1 (1%)	2 (2%)	0	0
Hyperkalaemia	0	0	0	0	2 (2%)	1 (1%)	0	0
Hypoxia	0	0	0	0	0	3 (3%)	0	0
Lower respiratory tract infection	0	0	0	0	2 (2%)	1 (1%)	0	0

(Table 2 continues on next page)

	Belantamab mafodotin 2·5 mg/kg group (n=95)				Belantamab mafodotin 3·4 mg/kg group (n=99)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Malaise	0	0	0	0	2 (2%)	1 (1%)	0	0
Wheezing	0	0	0	0	2 (2%)	1 (1%)	0	0
Increased blood creatine	0	0	0	0	1 (1%)	1 (1%)	0	0
Cognitive disorder	0	0	0	0	1 (1%)	1 (1%)	0	0
Escherichia bacteraemia	0	0	0	0	1 (1%)	1 (1%)	0	0
Hyperviscosity syndrome	0	0	0	0	0	2 (2%)	0	0
Influenza	0	0	0	0	0	2 (2%)	0	0
Osteolysis	0	0	0	0	0	2 (2%)	0	0
Pathological fracture	0	0	0	0	0	2 (2%)	0	0
Respiratory tract infection	0	0	0	0	1 (1%)	1 (1%)	0	0
Acute myeloid leukaemia	0	0	0	0	0	0	0	1 (1%)
Agitation	0	0	0	0	0	1 (1%)	0	0
Brain abscess	0	0	0	0	0	1 (1%)	0	0
Colitis	0	0	0	0	0	1 (1%)	0	0
Depressed level of consciousness	0	0	0	0	0	1 (1%)	0	0
Escherichia sepsis	0	0	0	0	0	1 (1%)	0	0
Lower gastrointestinal haemorrhage	0	0	0	0	0	1 (1%)	0	0
Haematochezia	0	0	0	0	0	1 (1%)	0	0
Haemophagocytic lymphohistiocytosis	0	0	0	0	0	0	0	1 (1%)
Lumbar spinal stenosis	0	0	0	0	0	1 (1%)	0	0
Nocardiosis	0	0	0	0	0	1 (1%)	0	0
Oesophagitis	0	0	0	0	0	1 (1%)	0	0
Otitis media	0	0	0	0	0	1 (1%)	0	0
Pancytopenia	0	0	0	0	0	1 (1%)	0	0
Pericardial effusion	0	0	0	0	0	1 (1%)	0	0
Pericarditis	0	0	0	0	0	1 (1%)	0	0
Influenzal pneumonia	0	0	0	0	0	1 (1%)	0	0
Pneumonia legionella	0	0	0	0	0	1 (1%)	0	0
Pneumonia respiratory syncytial viral	0	0	0	0	0	1 (1%)	0	0
Retinal vein occlusion	0	0	0	0	0	1 (1%)	0	0
Spinal osteoarthritis	0	0	0	0	0	1 (1%)	0	0
Upper limb fracture	0	0	0	0	0	1 (1%)	0	0

Grade 1–2 adverse events occurring in ≥10% of patients in either cohort, and all grade 3, 4, or 5 adverse events occurring in either cohort during treatment are reported. Data are number of patients (%). Listed in order of decreasing frequency of any grade events in the 2·5 mg/kg cohort. Events reported according to Common Terminology Criteria for Adverse Events criteria, version 4·03,[14] in the safety population (including all patients who received at least one dose of trial treatment), unless otherwise specified. *Keratopathy (based on eye examination, characterised as corneal epithelium changes with or without symptoms, considered an adverse event of special interest) was observed by ophthalmic examination. †Thrombocytopenia (considered an adverse event of special interest) includes the preferred terms thrombocytopenia, decreased platelet count, and cerebral haemorrhage. ‡Events occurring within 24 h of infusion are included for individual adverse events (preferred terms) and also counted within infusion-related reactions. §Blurred vision includes the preferred terms blurred vision, diplopia, reduced visual acuity, and visual impairment. ¶Infusion-related reactions (considered an adverse event of special interest) includes preferred terms infusion-related reaction, pyrexia, chills, diarrhoea, nausea, asthenia, hypertension, lethargy, tachycardia, vomiting, cough, and hypotension occurring within 24 h of infusion. ||Dry eye includes preferred terms dry eye, ocular discomfort, eye pruritus, and foreign body sensation in eye. **Neutropenia includes neutropenia, febrile neutropenia, and decreased neutrophil count.

Table 2: **Adverse events**

34 [77%] of 44 patients in the 3·4 mg/kg group). Among 22 participants in the 2·5 mg/kg group, with definite worsening of vision at the end of treatment, 15 [68%] recovered and seven [32%] were no longer in follow-up (because of sickness or unwillingness to come back for further examination). Among 22 participants in the 3·4 mg/kg group, with definite worsening of vision at the end of treatment, ten [45%] recovered and six [27%] were no longer in follow-up (because of sickness or unwillingness to come back for further examination). The median time to resolution after treatment exposure was 21·0 days (IQR 14–36) in the 2·5 mg/kg group and 63·5 days (23·0–127·0) in the 3·4 mg/kg group. Permanent loss of vision was not reported.

In the ocular substudy, 30 patients were enrolled (17 in the 2·5 mg/kg group and 13 in the 3·4 mg/kg group); however, post-baseline data were only available for 29 patients (17 in the 2·5 mg/kg group and 12 in the

3·4 mg/kg group). In the treated eye, grade 3 events occurred in five (29%) of 17 patients in the 2·5 mg/kg group and in five (42%) of 12 patients in the 3·4 mg/kg group. In the untreated eye, grade 3 events occurred in three (18%) of 17 patients in the 2·5 mg/kg group and in six (50%) of 12 patients in the 3·4 mg/kg group. Median time to keratopathy was similar between eyes treated with and without corticosteroid eye drops (24 [IQR 21–30] days with corticosteroid eye drops and 27 [21–42] days without in the 2·5 mg/kg cohort compared with 25 [9–40] days with corticosteroid eye drops and 25 [21–40] days without in the 3·4 mg/kg cohort).

Discussion

In DREAMM-2, belantamab mafodotin (2·5 mg/kg or 3·4 mg/kg) every 3 weeks showed clinically meaningful activity in patients with relapsed or refractory multiple myeloma. Overall responses were achieved in more than 30% of patients in each cohort and around 20% achieved a very good partial response or better. The depth and durability of responses seen with single-agent belantamab mafodotin in this population compares favourably with the responses described with other approved combination treatments for relapsed or refractory multiple myeloma.[2,10] In DREAMM-1, 60% of patients with heavily pre-treated relapsed or refractory multiple myeloma achieved an overall response with single-agent belantamab mafodotin (3·4 mg/kg every 3 weeks) and patient responses improved over time, contributing to prolonged progression-free survival and overall survival.[12,13] In a post-hoc analysis in DREAMM-2, the median duration of response in the overall patient population and overall survival in patients achieving an overall response (partial response or better) or a clinical benefit (minimal response or better) were not reached. These results suggest that clinical responses obtained with belantamab mafodotin treatment persist beyond the 6-month follow-up period for this primary analysis. To date, STORM is the only other clinical trial to prospectively evaluate an anti-myeloma treatment (selinexor plus dexamethasone) in patients refractory to proteasome inhibitors, immunomodulatory drugs, and daratumumab.[7] In that study, duration of response was 4·4 months, progression-free survival was 3·7 months, and overall survival was 8·6 months (15·6 months in patients with a clinical benefit or overall response).

A limitation of this primary analysis is the short duration of follow-up. Additional long-term follow-up of this ongoing study is needed to confirm the durability of responses. Additionally, a standard-of-care competitor arm was not included. When DREAMM-2 was initiated (study start date June 18, 2018), there were no published data on efficacy outcomes in patients who were refractory to both proteasome inhibitors and immunomodulatory drugs and exposed to anti-CD38 monoclonal antibodies. Although DREAMM-2 was not designed to compare between belantamab mafodotin doses or address non-inferiority, comparisons were made for exploratory purposes. The 2·5 mg/kg dose was selected as the recommended dose for future studies on the basis of its similar anti-myeloma activity with a more favourable safety profile (ie, less frequent dose modifications and a lower incidence of thrombocytopenia, bleeding, neutropenia, and infections) when compared with the 3·4 mg/kg dose.

In patients with multiple myeloma refractory to anti-CD38 monoclonal antibodies, responses to treatment and survival outcomes diminish with the failure of each subsequent regimen.[2] Anti-CD38 monoclonal antibodies are being increasingly used in newly diagnosed patients, therefore the number of patients with multiple myeloma refractory to anti-CD38 monoclonal antibodies is likely to increase, constituting an important population with unmet clinical need. In a large study of daratumumab-refractory patients with relapsed or refractory multiple myeloma, high-risk cytogenetic features and impaired renal function were predictive of poorer survival outcomes.[2] DREAMM-2 demonstrated that in small, prespecified subcohorts of patients with moderate renal impairment or high-risk cytogenetic features, a similar proportion of patients achieved an overall response to those in the overall population (although a lower proportion of patients with extramedullary disease at screening appeared to achieve an overall response than in the overall population), suggesting that these high-risk patients respond equally well to belantamab mafodotin. Longer-term follow-up is needed to establish whether these findings will confer an overall survival benefit.

Several BCMA-directed therapies are in clinical development, including chimeric antigen receptor T-cell (CAR-T) therapies and bi-specific antibodies.[17–21] CAR-T therapy studies have shown a high proportion of patients achieving an overall response; however, several challenges make this option unsuitable for patients with relapsed or refractory multiple myeloma who are unfit for the conditioning regimens or with inadequate disease control.[20,22] Thus, a high unmet medical need remains for these patients.[2,4] Belantamab mafodotin is the first anti-BCMA agent that offers the advantage of being a single agent with a multimodal novel mechanism of action, which is a practical treatment option that is applicable to a larger and more diverse relapsed or refractory multiple myeloma population.

Belantamab mafodotin appears to have a manageable safety profile with no new safety concerns identified in DREAMM-2 compared with DREAMM-1.[12,13] The incidence of grade 3–4 pneumonia and upper respiratory tract infections in patients was lower than previously reported[23] and comparable with that observed in DREAMM-1.[13] Furthermore, a meta-analysis of 13 trials found that monoclonal antibody treatment of relapsed or refractory multiple myeloma was associated with myelosuppression and this increased the risk of infections, including pneumonia.[24] Corneal epithelium

changes observed by ophthalmic examination were common in DREAMM-2; however, they were mostly restricted to the epithelium and few patients permanently discontinued treatment because of these events. Initial results from the ocular substudy suggest that corticosteroid eye drops were an ineffective prophylaxis for the development of changes to the corneal epithelium. Dose reductions and delays with concomitant use of preservative-free artificial tears were useful for management of these events. Patient-reported corneal symptoms were less frequent; however, they commonly occurred in patients with changes to the corneal epithelium, suggesting that patients with corneal epithelium changes are more likely to be symptomatic. The nature of corneal events reported for DREAMM-2 is not uncommon in antibody–drug conjugates, which use MMAF or other microtubule-targeting cytotoxins. The exact mechanism for the onset of corneal events is unknown; however, it might be related to non-specific uptake of the antibody–drug conjugate into actively dividing epithelial cells residing in the basal epithelial layer of the cornea.[25] Dose modifications (dose delays and dose reductions) should be considered to manage corneal events, as clinically warranted. If grade 2 reactions occur, the dose should be reduced by 25% and treatment continued. For grade 3 or 4 reactions, treatment should be withheld until symptoms have resolved to grade 2 or better and then dosing should be resumed at a 25% reduction. Once symptoms resolve to grade 1 or better, the dose can be increased to a starting dose. Thrombocytopenia and infusion-related reactions were also common, but considered self-limited.

Cardiotoxicity, peripheral neuropathy, and gastrointestinal and neutropenic adverse events have been described with selected proteasome inhibitors and immunomodulatory drugs, and for some patients dose modification for substantial renal impairment is required.[26,27] Treatment tolerability is an issue, as treatment discontinuation due to a proteasome inhibitor and adverse events related to immunomodulatory drugs lead to poorer clinical outcomes.[28] Few of these adverse events were reported with belantamab mafodotin in DREAMM-2. BCMA-targeted CAR-T therapies have reported a risk of cytokine release syndrome and neurotoxicity that were not observed with belantamab mafodotin.[20,22] Infusion-related reactions following belantamab mafodotin treatment are less frequent than have been reported with other agents, such as daratumumab, allowing omission of premedications.[29]

The mechanism of action and manageable safety profile of belantamab mafodotin make it a potential candidate for use in combination treatment regimens. Ongoing (NCT04091126) and planned trials will investigate belantamab mafodotin combinations with new and standard-of-care treatments. In conclusion, belantamab mafodotin shows anti-myeloma activity in patients with relapsed or refractory multiple myeloma, in particular those with heavily pretreated disease refractory to a proteasome inhibitor and immunomodulatory drug, and refractory or intolerant, or both, to an anti-CD38 monoclonal antibody.

Contributors

AB, AC, ADC, AKN, A-OA, AS, BA, CH, DS, EJD, ELi, HCL, HQ, KW, LK, KMK, NC, NL, PH, PM, PR, PR-O, PMV, RB, RP, SDE, ST, and TF contributed to acquisition of data. AH, EJD, ELe, EZ, IG, JB, JO, RCJ, SL, SZU, and TP contributed to study design and data analysis and interpretation. SL contributed to study conception and design. SZU contributed to data analysis. All authors were involved at each stage of manuscript preparation and approved the final version.

Declaration of interests

SL has received grant funding and personal fees from Celgene and Takeda, and personal fees from Novartis, Bristol-Myers Squibb, GlaxoSmithKline, Amgen, Merck, and Janssen. HCL has received grant funding and personal fees from Amgen, Celgene, Janssen, and Takeda; personal fees from GlaxoSmithKline and Sanofi, and grant funding from Daiichi Sankyo. ST has received grant funding and personal fees from Amgen, Celgene, Janssen, and GlaxoSmithKline, and personal fees from Takeda, Novartis, Sanofi, and Karyopharm. AKN has received grant funding and personal fees from GlaxoSmithKline, Janssen, Bristol-Myers Squibb, Celgene, Takeda, and Amgen; and personal fees from Oncopeptides and Spectrum. AC has received grant funding and personal fees from Janssen, Celgene, Novartis, Amgen, Seattle Genetics, and Millennium/Takeda; personal fees from Bristol-Myers Squibb, Karyopharm, Sanofi, Oncopeptides, and Antengene; and grant funding from Pharmacyclics. NL is currently a full-time employee of Janssen and in the past has received research funding from GlaxoSmithKline, Takeda, Karyopharm, Sanofi, and Amgen. DS has received personal fees from Celgene, Janssen, and Amgen. AS has received grant funding and personal fees from GlaxoSmithKline, Janssen Oncology, and Karyopharm, and grant funding from Bristol-Myers Squibb and Celgene. KW has received grant funding, personal fees, and non-financial support from Amgen, Celgene, Janssen, and Takeda; personal fees and non-financial support from Bristol-Myers Squibb; grant funding and non-financial support from Sanofi; and personal fees from Juno, Adaptive Biotech, and Karyopharm. LK has received personal fees for participation in advisory boards from Amgen, Janssen, Celgene, and Takeda, and travel support from Amgen and Janssen. ELi has received personal fees from AbbVie and Janssen, and research funding from Celgene, Genentech, Amgen, and GlaxoSmithKline. BA has received non-financial and other support from Sanofi and Takeda (travel to congress for Sanofi and Takeda; and participation in advisory board for Takeda), and personal fees and other support from Janssen, Celgene, Takeda, and Amgen (travel to congress and honoraria for Janssen, Celgene, and Amgen; and participation in advisory board for Celgene and Amgen). TF has received personal fees from Janssen, Celgene, Takeda, Amgen, Karyopharm, Oncopeptides, and Roche. CH has received personal fees from Celgene, Janssen, and Amgen. PR-O has received personal fees and non-financial support from Celgene and Janssen, and personal fees from Kite Pharma, Amgen, Sanofi, AbbVie, Bristol-Myers Squibb, and Oncopeptides. SZU has received grant funding and personal fees from Amgen, Celgene, Sanofi, Seattle Genetics, Janssen, Takeda, and SkylineDX; personal fees from AbbVie and MundiPharma, and grant funding from Bristol-Myers Squibb and Pharmacyclics. PH has received grant funding and personal fees from Celgene, Takeda, Janssen, and AbbVie; grant funding from GlaxoSmithKline, and personal fees from Bristol-Myers Squibb and Kite/Gilead. RB has received grant funding from Celgene, Karyopharm, Sanofi, Merck, Bristol-Myers Squibb, and AbbVie, and personal fees from GlaxoSmithKline. HQ has received grant funding from Celgene and Amgen; personal fees from GlaxoSmithKline, Karyopharm, Janssen and Takeda, and non-financial research support from Sanofi. PM has received personal fees from GlaxoSmithKline, Celgene, Amgen, and Takeda. PMV is a consultant for Amgen, Celgene, Janssen, Bristol-Myers Squibb, Novartis, Takeda, Oncopeptides, and Teneo-Bio, and has participated in speakers' bureaux for Amgen, Celgene, and Janssen. IG is an employee of and holds stocks and shares in GlaxoSmithKline and holds stocks and shares in Novartis. AH, JB, TP, RCJ, EJD, and JO are employees of and hold stocks and shares in

GlaxoSmithKline. EZ and ELe are employees of GlaxoSmithKline. RP has received grant funding, personal fees, and non-financial support from Takeda; personal fees and non-financial support from Janssen, Celgene, and GlaxoSmithKline, and personal fees from AbbVie. SDE has received personal fees from GlaxoSmithKline. PR has received grant funding and personal fees from Celgene, Takeda, and Oncopeptides; grant funding from Bristol-Myers Squibb, and personal fees from Janssen, Karyopharm, Amgen, and Sanofi. ADC has received grant funding from GlaxoSmithKline, Bristol-Myers Squibb, and Novartis; personal fees from Janssen, Takeda, Oncopeptides, Kite Pharma, and Seattle Genetics, and personal fees and other association with GlaxoSmithKline and Celgene. AB, KMK, A-OA, and NC declare no competing interests.

Data sharing

Information about GlaxoSmithKline's data sharing commitments and access requests to anonymised individual participant data and associated documents can be requested for further research from ClinicalStudyDataRequest.com.

Acknowledgments

This study was funded by GlaxoSmithKline. GlaxoSmithKline contributed to study design, implementation, data collection, interpretation and analysis. Medical writing support was funded by GlaxoSmithKline. We thank the ophthalmology and optometry colleagues who provide ophthalmic examinations to patients enrolled in the study, and Jeff Jackson, Karrie Wang, Joe Kovach, Kaytlyn Nungesser, and Alessandra Tosolini. Medical writing support was provided by Fiona Woodward, Chloe Stevenson, and Sarah Hauze, of Fishawack Indicia, UK, funded by GlaxoSmithKline. Drug linker technology was licensed from Seattle Genetics (Bothell, WA, USA) and the monoclonal antibody was produced with POTELLIGENT Technology licensed from BioWa (Princeton, NJ, USA). RP is supported by the National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre and this trial was supported in part by the NIHR UCLH Clinical Research Facility and the Cancer Research UK Experimental Cancer Medicine Centre.

References

1 Nooka AK, Lonial S. New targets and new agents in high-risk multiple myeloma. *Am Soc Clin Oncol Educ Book* 2016; **36:** e431–41.
2 Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia* 2019; **33:** 2266–75.
3 Neri P, Bahlis NJ, Lonial S. New strategies in multiple myeloma: immunotherapy as a novel approach to treat patients with multiple myeloma. *Clin Cancer Res* 2016; **22:** 5959–65.
4 Popat R, Brown SR, Flanagan L, et al. Bortezomib, thalidomide, dexamethasone, and panobinostat for patients with relapsed multiple myeloma (MUK-six): a multicentre, open-label, phase 1/2 trial. *Lancet Haematol* 2016; **3:** e572–80.
5 Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. *N Engl J Med* 2018; **379:** 1811–22.
6 Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. *Blood* 2017; **130:** 974–81.
7 Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. *N Engl J Med* 2019; **381:** 727–38.
8 Lee L, Bounds D, Paterson J, et al. Evaluation of B cell maturation antigen as a target for antibody drug conjugate mediated cytotoxicity in multiple myeloma. *Br J Haematol* 2016; **174:** 911–22.
9 O'Connor BP, Raman VS, Erickson LD, et al. BCMA is essential for the survival of long-lived bone marrow plasma cells. *J Clin Exp Med* 2004; **199:** 91–98.
10 Tai Y-T, Mayes PA, Acharya C, et al. Novel anti-B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. *Blood* 2014; **123:** 3128–38.
11 Montes De Oca R, Bhattacharya S, Vitali N, et al. The anti-BCMA antibody-drug conjugate GSK857916 drives immunogenic cell death and immune-mediated anti-tumor responses, and in combination with an Ox40 agonist potentiates in vivo activity. *HemaSphere* 2019; **3:** 231.
12 Trudel S, Lendvai N, Popat R, et al. Targeting B-cell maturation antigen with GSK2857916 antibody–drug conjugate in relapsed or refractory multiple myeloma (BMA117159): a dose escalation and expansion phase 1 trial. *Lancet Oncol* 2018; **19:** 1641–53.
13 Trudel S, Lendvai N, Popat R, et al. Antibody–drug conjugate, GSK2857916, in relapsed/refractory multiple myeloma: an update on safety and efficacy from dose expansion phase I study. *Blood Cancer J* 2019; **9:** 37.
14 National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Rockwell, MD: National Cancer Institute, 2009. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 (accessed Oct 14, 2019).
15 Eaton JS, Miller PE, Mannis MJ, Murphy CJ. Ocular adverse events associated with antibody–drug conjugates in human clinical trials. *J Ocul Pharmacol Ther* 2015; **31:** 589–604.
16 Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Cohort consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016; **17:** e328–46.
17 Gregory T, Cohen AD, Costello CL, et al. Efficacy and safety of P-BCMA-101 CAR-T cells in patients with relapsed/refractory (r/r) multiple myeloma (MM). *Blood* 2018; **132** (suppl 1): 1012.
18 Brudno JN, Maric I, Hartman SD, et al. T cells genetically modified to express an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma. *J Clin Oncol* 2018; **36:** 2267–80.
19 Cohen AD, Garfall AL, Stadtmauer EA, et al. B cell maturation antigen-specific CAR T cells are clinically active in multiple myeloma. *J Clin Invest* 2019; **129:** 2210–21.
20 Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. *N Engl J Med* 2019; **380:** 1726–37.
21 Topp MS, Duell J, Zugmaier G, et al. Evaluation of AMG 420, an anti-BCMA bispecific T-cell engager (BiTE) immunotherapy, in R/R multiple myeloma (MM) patients: updated results of a first-in-human (FIH) phase I dose escalation study. *Proc Am Soc Clin Oncol* 2019; **37** (suppl): 8007.
22 Zhao W-H, Liu J, Wang B-Y, et al. A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma. *J Hematol Oncol* 2018; **11:** 141.
23 Blimark C, Holmberg, E, Mellqvist, UH, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. *Haematol* 2015; **100:** 107–13.
24 Al-Jasser AN, Al Adwani NI. Bilateral thalamic lesions in hepatic encephalopathy. *Neurosciences* 2018; **23:** 165–67.
25 Zhao H, Atkinson J, Gulesserian S, et al. Modulation of macropinocytosis-mediated internalization decreases ocular toxicity of antibody-drug conjugates. *Cancer Res* 2018; **78:** 2115–26.
26 Cole DC, Frishman WH. Cardiovascular complications of proteasome inhibitors used in multiple myeloma. *Cardiol Rev* 2018; **26:** 122–29.
27 Ale A, Bruna J, Navarro X, Udina E. Neurotoxicity induced by antineoplastic proteasome inhibitors. *Neurotoxicology* 2014; **43:** 28–35.
28 Sonneveld P. Management of multiple myeloma in the relapsed/refractory patient. *ASH Education Program Book* 2017; **2017:** 508–17.
29 Nooka AK, Gleason C, Sargeant MO, et al. Managing infusion reactions to new monoclonal antibodies in multiple myeloma: daratumumab and elotuzumab. *J Oncol Pract* 2018; **14:** 414–22.

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