# Single-Agent Belantamab Mafodotin in Patients with Relapsed or Refractory Multiple Myeloma (RRMM): Final Analysis of the DREAMM-2 trial

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## Introduction

Belantamab mafodotin (belamaf) is a first-in-class, B-cell maturation antigen-binding (BCMA) antibody-drug conjugate containing monomethyl auristatin F (MMAF), which eliminates myeloma cells via a multimodal mechanism including direct cell kill and anti-myeloma immune response.[1-3]

## Objective

To analyze the efficacy/safety profile of belamaf using the final data from the DREAMM-2 trial (NCT03525678), which corresponds to an approximate 3-year follow-up.

## Methods

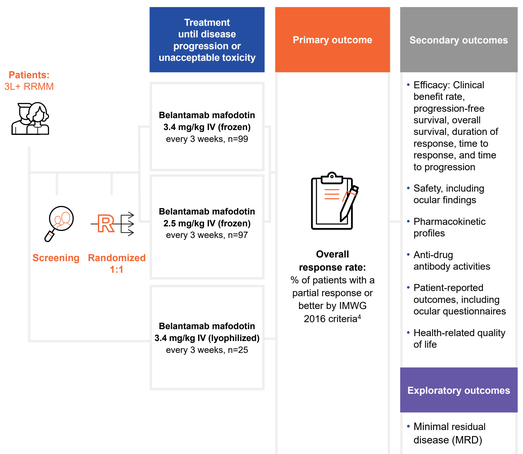
### Study design

DREAMM-2 was a Phase II, two-arm, open-label study of single-agent belamaf in patients with RRMM refractory to a PI, an immunomodulatory agent, and refractory or intolerant to an anti-CD38 mAb (**Figure 1**).

The study began in June 2018 and the last patient last visit was March 31, 2022.

**Figure 1. Study design**

**A Phase II, open-label, randomized, 2-dose study of belantamab mafodotin in patients with RRMM refractory to immunomodulatory drugs and proteasome inhibitors, and refractory/intolerant to an anti-CD38 monoclonal antibody (NCT03525678 and EudraCT: 2017-004810-25)**




**Eligibility criteria**

- Measurable disease*
- European Cooperative Oncology Group Performance Status of 0–2
- ≥3 prior lines of therapy
- Refractory to immunomodulatory drugs and proteasome inhibitors, and refractory/intolerant to an anti-CD38 monoclonal antibody
- Not exposed to a prior BCMA-targeted therapy
- Prior allogeneic stem cell transplant excluded

3L+, 3 or more lines of therapy; DREAMM, DRiving Excellence in Approaches to Multiple Myeloma; IMWG, International Myeloma Working Group; IV, intravenous; mAb, monoclonal antibody; MRD, minimal residual disease; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma
*Measurable disease defined as serum myeloma protein (M-protein) ≥0.5 g/dL; urine M-protein ≥200 mg/24h; serum free-light chain (FLC) assay – involved FLC level ≥10 mg/dL; and an abnormal serum FLC ratio (<0.26 or >1.65)

## Results

### Enrollment, demographics, and baseline clinical characteristics

In total, 221 patients were enrolled in the trial.

Full patient demographic and baseline characteristics have been previously reported.[1,5]

The median age of patients randomized to belamaf 2.5 mg/kg was 65 (IQR: 60–70) years, 67 (61–72) years for patients in the 3.4 mg/kg cohort, and 68 (46–89) years in the lyophilized cohort; 21% of the patients had extramedullary disease and 43% had high-risk cytogenetics.[5,6]

Patients had a median of 7 (2.5 mg/kg), 6 (3.4 mg/kg), or 5 (lyophilized) prior lines of therapy at baseline.

Overall, the main reasons for treatment discontinuation were progressive disease (belamaf 2.5 mg/kg: 73 patients; 3.4 mg/kg: 72 patients; lyophilized: 19 patients) and adverse events (2.5 mg/kg: 11 patients; 3.4 mg/kg: 12 patients; lyophilized: 2 patients)

- Post-analysis, 3 patients continued treatment with belamaf (2.5 mg/kg cohort: 1 patient; 3.4 mg/kg cohort: 2 patients)

There were 2 COVID-19 infection-related deaths during the study.

### Efficacy

Median follow-up was 12.5 (2.5 mg/kg), 13.8 (3.4 mg/kg), and 24.5 (lyophilized) months.

The ORR of 32% for the 2.5 mg/kg cohort remained consistent with previously reported data (**Table 1**).[5]

DoR improved to >12 months in the 2.5 mg/kg cohort from earlier reports.[5]

OS also improved to >15 months from the 13-month analysis.[5]

ORR, DoR, and CBR were maintained in subgroups with HR-cytogenetics, and mild–moderate renal impairment.

MRD negativity rate in patients achieving ≥VGPR remained consistent with previous reports.[5]

**Table 1. Key efficacy outcomes**

| Endpoint | 2.5 mg/kg cohort (N=97)* | 3.4 mg/kg cohort (N=99) |
|---|---|---|
| **ORR, % (97.5% CI)** | 32 (21.7–43.6) | 35 (24.8–47.0) |
| ≥CR (sCR + CR), n % | 9 (9) | 5 (5) |
| sCR, n % | 2 (2) | 3 (3) |
| CR, n % | 7 (7) | 2 (2) |
| VGPR, n % | 9 (9) | 19 (19) |
| PR, n % | 13 (13) | 11 (11) |
| MR, n % | 4 (4) | 5 (5) |
| SD, n % | 27 (28) | 22 (22) |
| **MRD-negativity rate for patients with ≥VGPR, % (95% CI)†** | 36 (12.8–64.9) | 23 (5.0–53.8) |
| ≥VGPR, n | 14 | 13 |
| MRD-negative, n | 5 | 3 |
| **Median time to response, months (95% CI)** | 1.5 (1.0–2.1) | 1.4 (0.9–2.1) |
| **Median DoR, months (95% CI)** | 12.5 (4.2–19.3) | 6.2 (4.8–18.7) |
| **Median PFS, months (95% CI)** | 2.8 (1.6–3.6) | 3.9 (2.0–5.8) |
| In ≥VGPR, months (95% CI)‡ | 14.0 (9.7–NR) | 16.8 (7.7–NR) |
| **Median OS, months (95% CI)** | 15.3 (9.9, 18.9) | 14.0 (10.0, 18.1) |
| In ≥VGPR, months (95% CI)‡ | 30.7 (19.7, 37.9) | 35.5 (14.1, NR) |

*Currently the only recommended EU dose as the 3.4 mg/kg dose was not further pursued; †MRD negativity was assessed by Next Generation Sequencing with a threshold of $10^{-5}$; ‡Post hoc analysis.

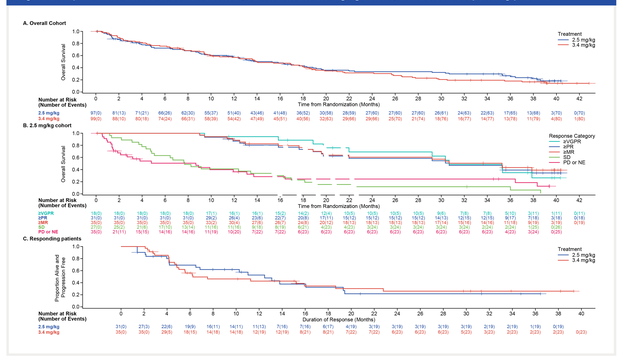
### Overall survival

Overall, median OS (95% CI) was 15.3 (9.9–18.9) months for the 2.5 mg/kg cohort and 14.0 (10.0–18.1) months for the 3.4 mg/kg cohort (**Figure 2**).

- In patients who achieved ≥VGPR, estimated OS was 30.7 (n=19, 20%) and 35.5 (n=24, 24%) months for the 2.5 and 3.4 mg/kg cohorts, respectively.
- In patients who achieved ≥VGPR, estimated median PFS was 14.0 and 16.8 months for the 2.5 and 3.4 mg/kg cohorts, respectively.

Median DoR (95% CI) was 12.5 months (4.2, 19.3) in the 2.5 mg/kg cohort and 6.2 months (4.8, 18.7) in the 3.4 mg/kg cohort.

**Figure 2. Kaplan-Meier curves of overall survival, survival in the 2.5 mg/kg cohort, and DoR for responding patients**




### Safety

No new safety signals were noted when comparing the incidence of AEs with earlier reports from this study (**Table 2**).[1,5]

The most commonly reported any-grade ocular AEs in both cohorts included keratopathy, blurred vision, and BCVA reduced to 20/50 or worse.

**Table 2. Safety outcomes**

| Outcome, n (%) | 2.5 mg/kg cohort (N=95) | 3.4 mg/kg cohort (N=99) |
|---|---|---|
| **Any-grade AEs, n (%)** | 93 (98) | 99 (100) |
| **Grade ≥3 AEs, n (%)** | 80 (84) | 82 (83) |
| **Most frequent AEs (any grade), n (%)** | | |
| Keratopathy* | 67 (71) | 74 (75) |
| Grade 3 | 28 (29) | 24 (24) |
| Grade 4 | 1 (1) | 1 (1) |
| Thrombocytopenia* | 36 (38) | 56 (57) |
| Grade 3 | 9 (9) | 9 (9) |
| Grade 4 | 12 (13) | 23 (23) |
| Anemia* | 26 (27) | 38 (38) |
| Grade 3 | 20 (21) | 25 (25) |
| Grade 4 | 0 (0) | 3 (3) |
| Blurred vision*† | 24 (25) | 36 (36) |
| Nausea* | 24 (25) | 32 (32) |
| Pyrexia* | 22 (23) | 25 (25) |
| BCVA reduced to 20/50 or worse | 46 (48) | 49 (49) |
| **Overall infection rate, n (%)** | 43 (45) | 54 (55) |
| **Grade ≥3 infections** | 19 (20) | 44 (44) |
| **Most frequent infections (any grade), n (%)** | | |
| Upper respiratory tract infection | 10 (11) | 22 (22) |
| Pneumonia | 9 (9) | 18 (18) |
| **SAEs, n (%)** | 43 (45) | 53 (54) |
| **Fatal SAEs, n (%)** | 4 (4) | 9 (9) |
| **Treatment related fatal SAEs, n (%)** | 1 (1) | 2 (2) |

*Defined by CTCAE. †Blurred vision includes the preferred terms vision blurred, diplopia, visual acuity reduced, and visual impairment

### Dose delays and dose reductions

AEs, including ocular events, were managed primarily with dose delays and dose reductions (**Table 3**).

In the 2.5 mg/kg cohort, 51 (54%) patients had AE-related dose delays.

- 15 (16%) patients had 3 or more dose delays.
- In responding patients (n=31), dose delays >63 days occurred in 16 (52%) patients.

In the 3.4 mg/kg cohort, 61 (62%) patients had AE-related dose delays.

- 20 (20%) patients had more than 3 dose delays.
- In responding patients (n=34), dose delays >63 days occurred in 19 (56%) patients.

AE-related dose reductions occurred in 34 (36%) and 44 (44%) of patients in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively.

**Table 3. Dose delays, reductions and discontinuations**

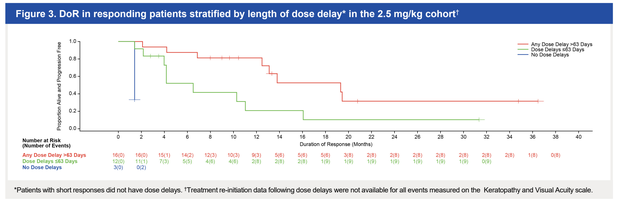
| Outcome, n (%) | 2.5 mg/kg cohort (N=95) | 3.4 mg/kg cohort (N=99) |
|---|---|---|
| **AE-related dose reductions, n (%)** | 34 (36) | 44 (44) |
| **Ocular AE-related dose reductions, n (%)** | | |
| Keratopathy | 27 (28) | 30 (30) |
| Blurred vision | 2 (2) | 3 (3) |
| Dry eye | 1 (1) | 0 (0) |
| **AE-related dose delays, n (%)** | 51 (54) | 61 (62) |
| **Ocular AE-related dose delays, n (%)** | | |
| Keratopathy | 45 (47) | 49 (49) |
| Blurred vision | 6 (6) | 13 (13) |
| Dry eye | 3 (3) | 3 (3) |
| Blepharitis | 0 (0) | 2 (2) |
| Eye pain | 0 (0) | 2 (2) |
| **AE-related permanent discontinuations, n (%)** | 11 (12) | 12 (12) |
| **Ocular AE-related permanent discontinuations, n (%)** | 5 (5) | 3 (3) |
| Keratopathy | 3 (3) | 3 (3) |
| Blurred vision | 1 (1) | 0 (0) |
| Visual acuity reduced | 1 (1) | 0 (0) |

### Effects of dose delays

Response was maintained in patients with dose delays >63 days (**Figure 3**).

Of the patients who had any keratopathy-related dose delay, 34 (76%) patients in the 2.5 mg/kg cohort and 39 (80%) patients in the 3.4 mg/kg cohort restarted treatment.

**Figure 3. DoR in responding patients stratified by length of dose delay* in the 2.5 mg/kg cohort†**




*Patients with short responses did not have dose delays. †Treatment re-initiation data following dose delays were not available for all events measured on the Keratopathy and Visual Acuity scale.

### Event resolution

Median time to resolution of the first event of blurred vision, reduced BCVA, and keratopathy was 43, 23, and 120 days, respectively, in the 2.5 mg/kg cohort (**Table 4**).

**Table 4. Resolution of ocular events**

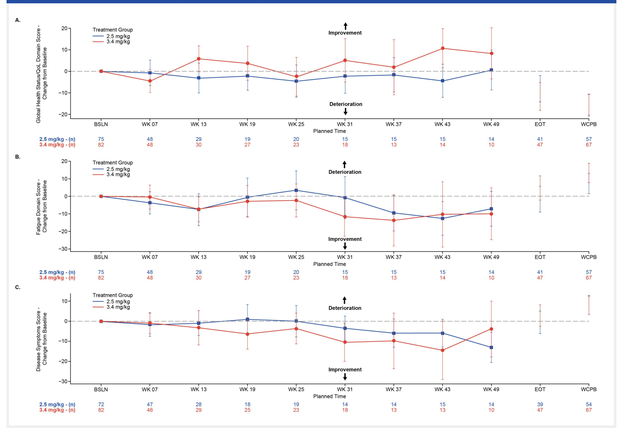
| Event | 2.5 mg/kg cohort (N=95) | 3.4 mg/kg cohort (N=99) |
|---|---|---|
| **Blurred vision** | | |
| Incidence | 24 (25) | 36 (36) |
| Patients in which AE has resolved, n (% patients with event) | 19 (79) | 32 (89) |
| Time to resolution of first event, days, median (range) | 43.0 (6–895) | 85.0 (1–568) |
| Not resolved, discontinued, follow-up ended, n (%) | 5 (21) | 4 (11) |
| **BCVA reduced to 20/50 or worse** | | |
| Incidence | 46 (48) | 49 (49) |
| Time to resolution of first BCVA event, days, median (range)* | 23.0 (5–103) | 44.0 (7–197) |
| Not resolved, discontinued, follow-up ended, n (%) | 6 (13) | 4 (8) |
| **Keratopathy** | | |
| Incidence, any grade, n (%) | 67 (71) | 74 (75) |
| Keratopathy time to resolution of first event, days, median (range)† | 120.0 (8–858) | 106.0 (8–841) |
| Not resolved, discontinued, follow-up ended, n (%) | 18 (27) | 27 (36) |

*Resolution defined as having a post-baseline score ≥20/50 or no equivalent value in either eye. †Duration defined as time from onset of any keratopathy event to first time subject is free from event. A gap of at least 1 day was required between resolution of 1st and occurrence of 2nd event.

### Health-related quality of life

EORTC-QLQ-C30 data suggested that overall global health status/QoL, physical and role functioning, and overall disease symptoms were maintained or improved during belamaf treatment (**Figure 4**).

**Figure 4. Global health status, fatigue, and disease symptoms**




## Conclusions

The clinically meaningful efficacy of belamaf from earlier (6- and 13-month)[1,5] analyses of the DREAMM-2 study was sustained at this 3-year timepoint in patients with triple-class refractory RRMM.

Patients who respond to belamaf (ORR 32% in the 2.5 mg/kg cohort) have a long DoR (12.5 months).

The OS and DoR observed in patients who achieved ≥VGPR is similar to those observed in trials for the CAR-T-cell therapy idecabtagene vicleucel.[6]

Dose modification remained effective in resolving ocular events, which are a known class effect of MMAF-containing antibody-drug conjugates.[7] Dose delays >63 days did not have detrimental effects on DoR and may increase tolerability of belamaf.

Despite the frequency of adverse events or the occurrence of ocular events, patients' HRQoL was largely unaffected.

**Overall, single-agent belamaf at a dose of 2.5 mg/kg Q3W results in rapid, deep, durable, and clinically meaningful responses with a manageable safety profile in patients with triple-class refractory RRMM, a patient population with otherwise poor prognosis and limited treatment options.**

## Abbreviations

AE, adverse event; BCMA, B-cell maturation antigen; BCVA, best corrected visual acuity; belamaf, belantamab mafodotin; CAR-T, chimeric antigen receptor T-cell therapy; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DoR, duration of response; DREAMM, DRiving Excellence in Approaches to Multiple Myeloma; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; HRQoL, health-related quality of life; IMWG, International Myeloma Working Group; IQR, interquartile range; ITT, intention to treat; IV, intravenously; mAb, monoclonal antibody; MM, multiple myeloma; MMAF, monomethyl auristatin F; MR, minimal response; MRD, minimal residual disease; NE, non-estimable; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; QoL, quality of life; QR, Quick Response; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

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Yamile Coto-De Pani is a GSK employee and holds GSK stocks and shares.

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