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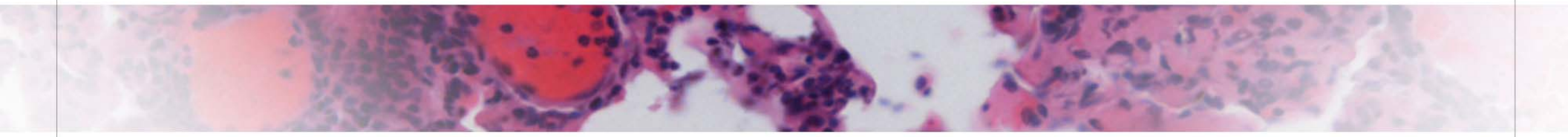

DREAMM-6: Safety, Tolerability, and Clinical Activity of Belantamab Mafodotin (Belamaf) in Combination with Bortezomib/Dexamethasone (Vd) in Relapsed/Refractory Multiple Myeloma (RRMM)

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Background

Belantamab mafodotin (belamaf; BLENREP) is a first-in-class BCMA-targeting, humanized, afucosylated ADC[1,2] approved in the US and the EU[3,4]

Belamaf eliminates myeloma cells by a multimodal mechanism involving ADC-mediated apoptosis, immune-dependent mechanisms of action such as ADCC/ADCP[1,2] and release of immunogenic cell-death markers[5] that may lead to an adaptive immune response

In the pivotal Phase II DREAMM-2 study (NCT03525678) single-agent belamaf demonstrated deep and durable clinical responses in patients with RRMM[6,7]

- At 13 months of follow-up responses with belamaf (2.5 mg/kg; IV Q3W) were sustained (ORR was 32%, estimated median DoR and OS were 11.0 months and 13.7 months, respectively)*[7]
    - At the time of data cut-off, 10% (10/97) patients were still on study treatment
- DREAMM-2 included patients who were refractory to an immunomodulatory drug and a proteasome inhibitor, and refractory to and/or intolerant to an anti-CD38 mAb[6]

Management strategies for RRMM now prioritize combination therapies using agents with differing mechanisms of action to achieve synergistic effects and maximize efficacy[8,9]

A multimodal anti-tumor mode of action and an acceptable safety profile make belamaf a promising new therapy for use in RRMM combination regimens with both proteasome inhibitors and immunomodulatory drugs

Pre-clinical data suggest increased anti-myeloma activity and survival benefit upon belamaf combination with bortezomib (Velcade) and/or dexamethasone (Vd) above single agents[10]

Aims:

To present preliminary data on the safety and efficacy of 2.5 mg/kg belamaf administered as a single dose in combination with a standard-of-care regimen of Vd, from the DREAMM-6 (NCT03544281) study in patients with RRMM

*Belamaf 3.4 mg/kg ORR was 35%, estimated median DoR was 6.2 months, and the estimated median OS was 13.8 months.

ADC, antibody-drug conjugate; ADCC/ADCP, antibody-dependent cellular cytotoxicity/phagocytosis; belamaf, belantamab mafodotin; BCMA, B-cell maturation antigen; DoR, duration of response; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; Q3W, every 3 weeks; RRMM, relapsed/refractory multiple myeloma; Vd, bortezomib plus dexamethasone.

1. Tai YT, Anderson KC. *Immunotherapy*. 2015;7:1187–99; 2. Tai YT, et al. *Blood*. 2014;123:3128–38; 3. BLENREP Prescribing Information; 4. BLENREP SmPC; 5. Montes De Oca R, et al. EHA 2019, Poster PF558; 6. Lonial S, et al. *Lancet Oncol*. 2020;21:207–21; 7. Lonial S, et al. ASCO 2020, Poster 436; 8. Moreau P, et al. *Ann Oncol*. 2017;28 (suppl 4):v52–61; 9. Nooka AK, Lonial S. *Oncology*. 2016;30:451–65; 10. Montes De Oca R, et al. AACR 2020, Poster 6711.

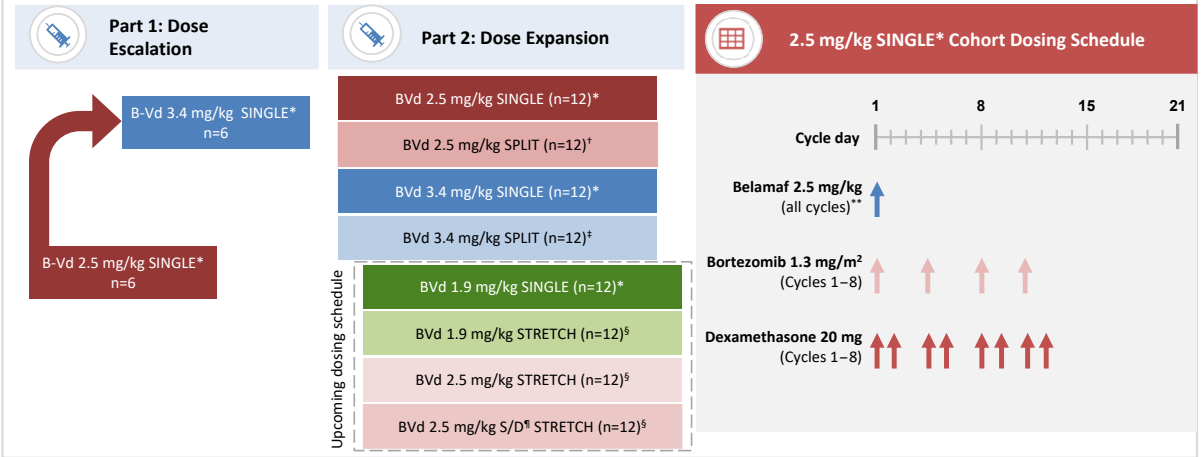
Methods

Study design: Arm B – belamaf 2.5 mg/kg SINGLE plus Vd

DREAMM-6 is an ongoing, two-arm, two-part, Phase I/II study evaluating the safety, tolerability, and clinical activity of belamaf in combination with lenalidomide/dexamethasone (Arm A) or Vd (Arm B), in patients with RRMM[1]

- Arm B: Part 1 (dose escalation) and Part 2 (dose expansion) evaluated belamaf (2.5 or 3.4 mg/kg; Q3W) administered as a SINGLE (full dose given on Day 1) or SPLIT dose (divided equally on Days 1 and 8) in combination with Vd for the first 8 cycles, followed by belamaf monotherapy until PD (**Figure 1**)

Figure 1. DREAMM-6 Arm B (belamaf plus Vd) study design



Key eligibility criteria

- At least 1 prior therapy
- Measurable disease††
- Adequate organ system function
- Prior autologous-stem cell transplant, or transplant-ineligible
- Patients refractory to bortezomib were not excluded
- ECOG PS 0–2
- Not exposed to a mAb within 30 days
- No prior treatment with investigational agent or systemic anti-myeloma therapy within 14 days (or 5 half-lives, whichever is shorter), or plasmapheresis within 7 days
- Written informed consent

*Full assigned belamaf dose administered on Day 1 of any 21-day cycle; †Belamaf 1.25 mg/kg on Day 1 and 1.25 mg/kg on Day 8 of any 21-day cycle; ‡Belamaf 1.7 mg/kg on Day 1 and 1.7 mg/kg on Day 8 of any 21-day cycle; §Belamaf will be administered prior to Vd as a single dose on Day 1 of every alternate 21-day cycle; ¶Belamaf will be administered prior to Vd as a 2.5 mg/kg dose on Day 1 of Cycle 1 followed by subsequent doses of 1.9 mg/kg starting on Day 1 of alternate 21-day cycles; **Combination treatment continued for up to 8 cycles; thereafter, patients could continue on single-agent belamaf until PD, unacceptable toxicity or consent being withdrawn; ††Serum myeloma protein (M-protein) ≥0.5 g/dL and/or urine M-protein ≥200 mg/24 h and/or serum free-light chain (FLC) assay: Involved FLC level ≥10 mg/dL and an abnormal serum FLC ratio (<0.26 or >1.65).
Belamaf, belantamab mafodotin; BVd, belamaf/bortezomib/dexamethasone; ECOG PS, Easter Cooperative Oncology Group performance status; mAb, monoclonal antibody; S/D, step-down; PD, disease progression; Q3W, every 3 weeks; RRMM, relapsed/refractory multiple myeloma; Vd, bortezomib plus dexamethasone.

1. Nooka A, et al. ASCO 2020, oral presentation.

Methods

Objectives and analyses: Arm B – belamaf 2.5 mg/kg SINGLE plus Vd

The **primary objectives** of the DREAMM-6 study are safety, tolerability, and clinical activity as measured by ORR (% of participants achieving ≥ PR as per IMWG Uniform Response Criteria for MM 2016[1]) for belamaf in combination with Vd

Dose reductions or delays were permitted for all treatments to manage AEs

AESI included corneal events (encompasses many preferred terms: symptoms related to corneal events such as blurred vision, and dry eye and keratopathy [MECs; changes in the corneal epithelium observed on eye examination, with or without patient-reported symptoms]), thrombocytopenia, and IRR

- A protocol-defined scale was used to grade keratopathy (MECs), ophthalmic examinations were performed by an ophthalmologist (or an optometrist if an ophthalmologist was not available)
- Investigator grading per CTCAE[2] was used for corneal events other than keratopathy (MECs), thrombocytopenia, and IRR

Analysis

Descriptive preliminary data are presented for the **Arm B belamaf 2.5 mg/kg SINGLE dose plus Vd groups from Parts 1 and 2 combined**, which are sufficiently mature to allow preliminary observations to be made

Data for other arms, dosing schedules, and doses are not mature and therefore not presented here (**Figure 1**)

AE, adverse events; AESI, adverse events of special interest; belamaf, belantamab mafodotin; IMWG, International Myeloma Working Group; IRR, infusion-related reaction; MEC, microcyst-like epithelial change; MM, multiple myeloma; NCI-CTCAE, National Cancer Institute-Common Toxicity Criteria for Adverse Events; ORR, overall response rate; PR, partial response; Vd, bortezomib plus dexamethasone.

1. Kumar S, et al. *Lancet Oncol.* 2016;17:e328–46; 2. Common Terminology Criteria for Adverse Events (CTCAE) National Cancer Institute 2010 https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf [accessed May 14 2020].

Results

Baseline characteristics: Arm B – belamaf 2.5 mg/kg SINGLE plus Vd

Belamaf plus Vd combination was administered to 18 patients with RRMM

As of May 5, 2020:

A total of 18 patients have received belamaf 2.5 mg/kg SINGLE plus Vd in Parts 1 and 2 of Arm B

- Part 1 has enrolled 6 patients
- Part 2 has enrolled 12 patients

Patient demographics and baseline disease characteristics are shown in **Table 1**

Table 1. Patient demographics and baseline disease characteristics

Characteristic	Belamaf 2.5 mg/kg SINGLE + Vd (n=18)
Age, years; median (range)	67 (47–83)
Sex, n (%)	
Male	11 (61)
Female	7 (39)
Race, n (%)	
African-American	4 (22)
Asian	2 (11)
White	12 (67)
ISS Stage, n (%)	
I	4 (22)
II	8 (44)
III	3 (17)
Unknown	3 (17)
ECOG PS, n (%)	
0–1	15 (83)
2	3 (17)
High-risk cytogenetics, n (%)*	5† (28)
Extramedullary disease, n (%)	
Yes	5 (28)
Prior lines of therapy, median (range)	3 (1–11)
Prior bortezomib therapy, n (%)‡	16 (89)
Prior daratumumab therapy, n (%)	9 (50%)

*t(4;14), t(14;16), or del17p13; †Cytogenetic data were not available for 6 patients; ‡Bortezomib refractory status was not collected systematically.
Belamaf, belantamab mafodotin; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; RRMM, relapsed/refractory multiple myeloma; Vd, bortezomib plus dexamethasone.

Results

Safety: Arm B – belamaf 2.5 mg/kg SINGLE plus Vd

Acceptable safety profile of belamaf plus Vd combination

At data cut-off, patients had a median (range) duration of exposure to belamaf of 25.5 (6.4–46.4) weeks, with no DLTs reported during the dose escalation phase

AEs were reported by all 18 patients (100%) (**Table 2**)

SAEs occurred in 13/18 (72%) patients; none were fatal

- SAEs considered related to study treatment occurred in 5 patients; 4/5 related to belamaf

Four patients permanently discontinued a study treatment due to AEs, of whom 3 discontinued bortezomib, and 4 discontinued dexamethasone; no patients discontinued belamaf

Dose reductions (in 15/18 [83%] patients) and delays (in 18/18 [100%] patients) were used to manage AEs

Table 2. Overview of Adverse Events

Patients with AE, n (%)	Belamaf 2.5 mg/kg SINGLE + Vd (n=18)
AEs related to any study treatment	18 (100)
Grade 3–4 AE	18 (100)
AEs leading to permanent discontinuation of a study treatment	4 (22)
AEs leading to permanent discontinuation of belamaf	0
AE leading to dose reductions	15 (83)
Keratopathy (MEC)	7 (39)
Thrombocytopenia	5 (28)
AE leading to dose interruption/delay	18 (100)
Keratopathy (MEC)	15 (83)
Thrombocytopenia	7 (39)
Any SAE	13 (72)
Fatal SAE	0
SAE related to study treatment	5 (28)

AE, adverse event; AESI, adverse events of special interest; belamaf, belantamab mafodotin; DLT, dose-limiting toxicity; MEC, microcyst-like epithelial change; SAE, serious adverse event; Vd, bortezomib plus dexamethasone.

Results

Safety (cont.): Arm B – belamaf 2.5 mg/kg SINGLE plus Vd

Thrombocytopenia and corneal events were managed with dose modifications

Maximum grade for AESI are shown in **Figure 2**

Three patients (17%) experienced Grade 2 **IRR** (per CTCAE); 2 patients had 1 event each and 1 patient had 3 events. Neither dose modification nor delay was required and treatment was not discontinued for any IRR event

Thrombocytopenia, per CTCAE (all grades) occurred in 14 patients (78%), leading to a dose reduction in 5 patients and a dose delay in 7 patients, but no discontinuations

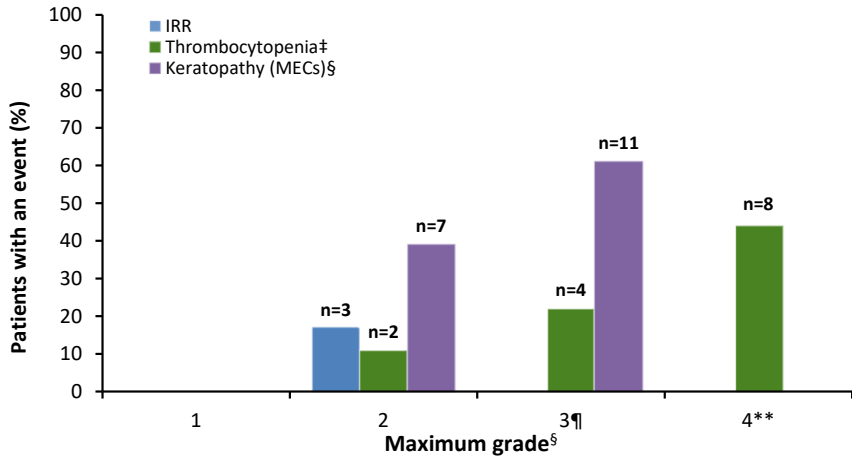
Keratopathy events, per a protocol-defined scale were reported in all patients[1–3]

- 11/18 patients (61%) had Grade 3 event*
- No patient permanently discontinued belamaf treatment due to keratopathy and all events were manageable with dose delays/reductions†

Blurred vision, per CTCAE (all grades) occurred in 12 patients (67%); 5 (28%) at Grade 3
Dry eye, per CTCAE occurred in 4 patients (22%; all Grade ≤2)

Peripheral neuropathy , per CTCAE was reported in 6 patients (33%; all Grade ≤2)

Figure 2. AESI by maximum grade



*For Grade 3 events, after holding the dose for the first instance, upon improvement of either visual acuity or ophthalmic exam findings to Grade 1 or baseline, dosing was resumed at 25% dose reduction; †For Grade 2 events, the dose was held if both the exam findings and visual acuity was Grade 2; once either of those improved to Grade 1, dosing was resumed at the current dose; ‡Thrombocytopenia includes MedDRA preferred terms platelet count decreased, thrombocytopenia; §Keratopathy (MECs) were defined using a protocol-defined scale; thrombocytopenia, IRR, and corneal events other than keratopathy (MECs) were defined using CTCAE v4.03[4] scale; ¶Grade 3: Severe or medically significant but not immediately sight-threatening, hospitalization or prolongation of existing hospitalization indicated, limiting self-care or activities of daily living; **Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye.

AESI, adverse event of special interest; belamaf, belantamab mafodotin; CTCAE, Common Toxicity Criteria for Adverse Events; IRR, infusion-related reaction; MECs, microcyst-like epithelial change; MedDRA, Medical Dictionary for Regulatory Activities Terminology; Vd, bortezomib plus dexamethasone.

1. Lonial S, et al. *Lancet Oncol.* 2020;21:207–21; 2. Lonial S, et al. EHA 2020, Poster EP970; 3. Farooq AV, et al. *Ophthalmol Ther.* 2020; doi: 10.1007/s40123-020-00280-8; 4. Common Terminology Criteria for Adverse Events (CTCAE) National Cancer Institute 2010 https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE4.03_2010-06-14_QuickReference_8.5x11.pdf [accessed May 14 2020].

Results

Investigator-assessed best confirmed response: Arm B – belamaf 2.5 mg/kg SINGLE plus Vd

Combination of belamaf plus Vd induces deep responses

All patients were evaluable for response assessment

The **ORR** for single-dose belamaf 2.5 mg/kg plus Vd was **78%** (14/18 patients; 95% CI: 52.4–93.6) (**Figure 3**)

- Patients with prior bortezomib or daratumumab exposure had an ORR of 75% (12/16 patients; 95% CI: 47.6–92.7) or 67% (6/9 patients; 95% CI: 29.9–92.5), respectively

CBR (≥ MR) was **83%** (95% CI: 58.6–96.4), including 81% (95% CI: 54.4–96.0) and 67% (6/9 patients; 95% CI: 29.9–92.5) for patients with prior bortezomib and daratumumab exposure, respectively

VGPR or better was achieved by **67%** (12/18 patients), including 63% (10/16) and 44% (4/9) patients with prior bortezomib and daratumumab exposure, respectively

- sCR was achieved by 6% (1/18 patients)
- Patients who received only 1 prior LOT benefited the most; all (4/4) patients with LOT1 achieved VGPR or better vs. half (4/8) of those with LOT3+ (**Figure 4**)

At data cut-off, median DoR had not yet been reached

Figure 3. Investigator-assessed* best confirmed response

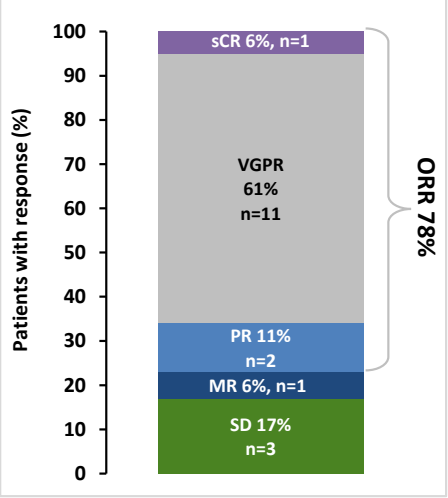
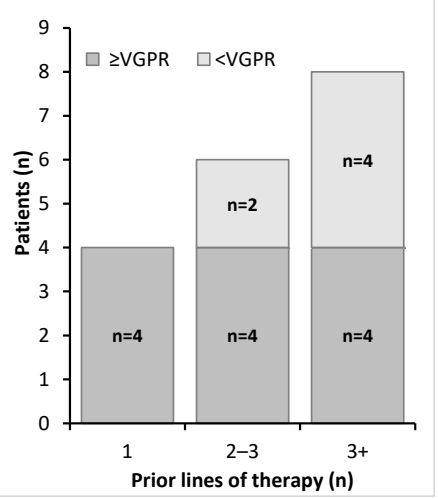


Figure 4. Investigator-assessed* best confirmed response per prior number of LOT



*Investigator-assessed best confirmed response per International Myeloma Working Group [IMWG] Uniform Response Criteria for MM 2016.[1]
Belamaf, belantamab mafodotin; CBR, clinical benefit rate; CI, confidence interval; DoR, duration of response; LOT, lines of treatment; MR, minimal response; ORR, overall response rate; PR, partial response; SD, stable disease; sCR, stringent complete response; Vd, bortezomib plus dexamethasone; VGPR, very good partial response.

1. Kumar S, et al. *Lancet Oncol.* 2016;17:e328–46.

Conclusions

Arm B – belamaf 2.5 mg/kg SINGLE plus Vd

Combination of belamaf with Vd has an acceptable safety profile and promising efficacy

The combination of belamaf 2.5 mg/kg Q3W with standard-of care Vd demonstrated an acceptable safety profile in patients with RRMM who had received a median of 3 prior lines of therapy (most patients had prior exposure to bortezomib and half to daratumumab), with AEs as expected, and no new safety signals to date

- Corneal events were common but manageable with belamaf dose modifications and dose delays
- Dose modifications and dose delays did not appear to impact clinical responses
- None of the patients discontinued belamaf

Investigator-assessed best response data demonstrated an ORR of 78%, with ≥VGPR of 67% (including sCR of 6%) and a CBR of 83%

The presented data support Phase III studies for the potential adoption of this combination for early-line use in the treatment paradigm

This study is currently ongoing. Data for Arm A and other cohorts of Arm B will be presented at future congresses

The BCMA-targeting MoA of belamaf supports combination with other therapies, including Vd, offering the potential for a manageable safety profile with enhanced efficacy

Belamaf is being evaluated in other combination strategies in various MM settings (poster 2299, 3247, and 2302 at this meeting). Further analyses of the pivotal DREAMM-2 study of single-agent belamaf are presented at this meeting (posters 1417, 2278, 3221, 3224, 3248)

AE, adverse event; BCMA, B-cell maturation antigen; belamaf, belantamab mafodotin; CBR, clinical benefit rate; MM, multiple myeloma; MoA, mode of action; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; Q3W, every 3 weeks; Vd, bortezomib plus dexamethasone; VGPR, very good partial response.

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