Safety and Clinical Activity of Belantamab Mafodotin With Lenalidomide Plus Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma: DREAMM-6 Arm-A Interim Analysis

Poster No. 441

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Background

Belantamab mafodotin (belamaf), a B-cell maturation antigen (BCMA)-targeting antibody-drug conjugate, has a multimodal mechanism of action that eliminates multiple myeloma (MM) cells via direct cytotoxicity as well as by a systemic anti-MM tumor immune response.[1-3]

Belamaf 2.5 mg/kg Q3W is the only BCMA-targeted ADC monotherapy approved for the treatment of patients with triple class refractory/exposed MM.[4,5]

In the pivotal Phase II DREAMM-2 study, single-agent belamaf (2.5 mg/kg Q3W) demonstrated deep and durable responses (ORR 32%, median duration of response of 11.0 months, and median overall survival of 13.7 months), in patients with RRMM.[6,7]

Preclinical data demonstrate synergy between belamaf and the immunomodulatory drug, lenalidomide (Len), suggesting an added benefit when combined with standard of care therapies such as Len + dexamethasone (Dex).[1,2]

Aims

To evaluate the safety and tolerability of belamaf in combination with Len/Dex in patients with RRMM.

Identify a belamaf dose/schedule with an improved benefit/risk profile to support further investigation in potential Phase III studies in patients with MM.

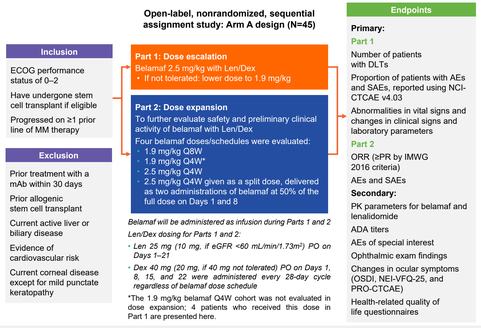
Methods

Study design

DREAMM-6 (NCT03544281) is an ongoing, two-part, two-arm, open-label, dose and schedule evaluation study, in which Arm A is assessing belamaf + Len/Dex in patients with RRMM who had previously received ≥1 line of therapy (LOT). A detailed study design is shown in **Figure 1**.

- ORR was assessed by the investigator per the International Myeloma Working Group (IMWG) 2016 criteria.[8]
- Adverse events, including keratopathy, were evaluated by the investigator according to the NCI-CTCAE v4.03.

Figure 1. DREAMM-6 study design



DLT, dose-limiting toxicity; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; FLC, free light chain; Ig, immunoglobulin; IMWG, International Myeloma Working Group; ISS, International Staging System; Len, lenalidomide; LOT, line of therapy; mAb, monoclonal antibody; MM, multiple myeloma; MMAF, monomethyl auristatin F; MR, moderate response; NEI-VFQ-25, National Eye Institute Visual Function Questionnaire; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reached; ORR, overall response rate; OSDI, Ocular Symptom Disease Index; PD, progressive disease; PK, pharmacokinetics; PO, by mouth; PR, partial response; PRO, patient-reported outcomes; RRMM, relapsed/refractory multiple myeloma; Q3W, every 3 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; SAE, serious adverse event; sCR, stringent complete response; SD, stable disease; SFLC, serum FLC; VGPR, very good partial response.

Results

Patient population

At the data cutoff (July 23, 2021), 45 patients received ≥1 dose (12 at 1.9 mg/kg Q8W; 4 at 1.9 mg/kg Q4W; 16 at 2.5 mg/kg Q4W; 13 at 2.5 mg/kg Q4W [split]).

Demographics and clinical characteristics of these patients are presented in **Table 1**.

- Median age was 68 years (range: 36–80).
- 29% (n=13) had high-risk cytogenetics defined as t(4;14), t(14;16), and/or 17p13del.
- 13% (n=6) had extramedullary disease.
- The median duration of follow-up varied across cohorts, with an overall median of 11.47 months (range: 0.5–31.1); of note, the 1.9 mg/kg Q8W cohort had the shortest median follow-up at 3.37 months (range: 0.5–6.5).
- Median prior LOT was 3 (range: 1–11) and 26 (58%) had prior Len treatment.

Table 1. Demographics, baseline disease, and clinical characteristics for patients treated with belamaf + Len/Dex

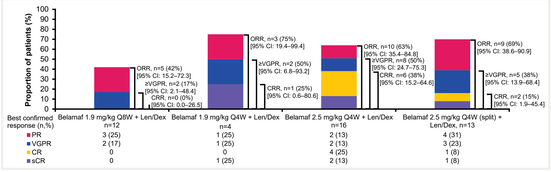
	Belamaf 1.9 mg/kg Q8W + Len/Dex n=12	Belamaf 1.9 mg/kg Q4W + Len/Dex n=4	Belamaf 2.5 mg/kg Q4W + Len/Dex n=16	Belamaf 2.5 mg/kg Q4W (split) + Len/Dex n=13	Total Population N=45
Age, years; median (range)	71.5 (48–76)	63.5 (53–66)	68.0 (55–80)	68.0 (36–75)	68.0 (36–80)
Male, n (%)	10 (83)	4 (100)	13 (81)	8 (62)	35 (78)
ECOG status at screening, n (%)					
0	5 (42)	4 (100)	5 (31)	4 (31)	18 (40)
1	7 (58)	0	9 (56)	9 (69)	25 (56)
2	0	0	2 (13)	0	2 (4)
ISS stage at screening, n (%)					
I	2 (17)	2 (50)	7 (44)	6 (46)	17 (38)
II	6 (50)	1 (25)	4 (25)	2 (15)	3 (29)
III	0	0	2 (13)	4 (31)	6 (13)
Unknown	4 (33)	1 (25)	3 (19)	1 (8)	9 (20)
Immunoglobulin, n (%)					
IgA	3 (25)	0	2 (13)	2 (15)	7 (16)
IgG	11 (92)	3 (75)	12 (75)	11 (85)	37 (82)
IgM	1 (8)	0	0	0	1 (2)
Other	0	0	1 (6)	0	1 (2)
Missing	0	1 (25)	1 (6)	0	2 (4)
Extramedullary disease, n (%)	2 (17)	0	3 (19)	1 (8)	6 (13)
High-risk cytogenetics, n (%)	2 (17)	0	5 (31)	6 (46)	13 (29)
Prior LOT, median (range)	3 (1–6)	2 (1–11)	2 (1–10)	3 (1–7)	3 (1–11)
Prior exposure to anti-MM therapies*, n (%)					
Chemotherapy	11 (92)	4 (100)	14 (88)	13 (100)	–
Immunomodulatory drug	11 (92)	3 (75)	14 (88)	9 (69)	–
Lenalidomide	7 (58)	1 (25)	10 (63)	8 (62)	–
Anti-CD38 monoclonal antibody	3 (25)	1 (25)	5 (31)	7 (54)	–
Proteasome inhibitor	10 (83)	4 (100)	15 (94)	13 (100)	–
Autologous stem cell transplant	6 (50)	0	3 (19)	4 (31)	–
Corticosteroids†	12 (100)	4 (100)	15 (94)	13 (100)	–
Relative dose intensity‡, %					
Belamaf	95.6	70.6	61.3	65.0	–
Lenalidomide	86.4	73.8	73.3	75.5	–
Duration of follow-up in months, median (range)	3.37 (0.5–6.5)	17.40 (15.2–22.4)	16.20 (0.5–31.1)	12.02 (2.0–16.3)	11.47 (0.5–31.1)

Patients may have received more than one class of anti-MM therapy. †All patients who received corticosteroids had received dexamethasone, and some received additional corticosteroids. ‡Relative dose intensity was defined as 100 (mean overall dose intensity divided by planned dose intensity) and reported as a percentage.

Investigator assessment of efficacy

ORR was 42% in the 1.9 mg/kg Q8W cohort (possibly due to shorter follow-up), 75% in the 1.9 mg/kg Q4W cohort, 63% in the 2.5 mg/kg Q4W cohort, and 69% in the 2.5 mg/kg Q4W (split) cohort (**Figure 2**).

Figure 2. Best confirmed response assessed by investigator



The median DOR was only reached in the 1.9 mg/kg Q4W cohort (11.1 mo [95% CI: 3.7–not reached [NR]). At the time of data cutoff, median progression-free survival was not reached in the 1.9 mg/kg Q8W or 2.5 mg/kg Q4W cohorts (**Table 2**).

Table 2. Duration of follow-up, duration of response, time to response, and progression-free survival

Outcome, months	Belamaf 1.9 mg/kg Q8W + Len/Dex, n=12	Belamaf 1.9 mg/kg Q4W + Len/Dex, n=4	Belamaf 2.5 mg/kg Q4W + Len/Dex, n=16	Belamaf 2.5 mg/kg Q4W (split) + Len/Dex, n=13
Duration of follow-up, median (range)	3.4 (0.5–6.5)	17.4 (15.2–22.4)	16.2 (0.5–31.1)	12.0 (2.0–16.3)
Duration of response*, median (95% CI)	NR (NR–NR)	11.1 (3.7–NR)	NR (2.6–NR)	NR (3.8–NR)
Time to response, median (95% CI)	1.0 (0.9–2.8)	1.0 (0.9–1.4)	1.0 (0.9–1.9)	1.9 (1.0–3.0)
Progression-free survival†, median (95% CI)	NR (0.9–NR)	8.6 (1.0–NR)	NR (1.9–NR)	9.0 (3.2–NR)

*Duration of response is defined as the time from the first documented evidence of confirmed PR or better until the time when confirmed disease progression is documented as per IMWG; †Progression-free survival is defined as the time from the first dose until the earliest date of confirmed PD per IMWG, or death due to any cause.

Safety

Across all cohorts, all patients experienced an adverse event (AE), with nearly all considered related to study treatment (**Table 3**).

Grade ≥3 AEs related to study treatment occurred at different rates across the cohorts, with lower rates in the 1.9 mg/kg Q8W and Q4W cohorts (42% and 50%, respectively) versus the 2.5 mg/kg Q4W cohorts with and without split dosing (85% and 81%, respectively).

Keratopathy (as graded by the CTCAE scale) was the most common AE of any grade across all cohorts.

- Grade ≥3 keratopathy occurred in no patients in the 1.9 mg/kg Q8W cohort (possibly due to shorter follow-up), 1 patient (25%) in the 1.9 mg/kg Q4W cohort, 8 patients (50%) in the 2.5 mg/kg Q4W cohort, and 6 patients (46%) in the 2.5 mg/kg Q4W (split) cohort.

In the 2.5 mg/kg Q4W (split) cohort, 4 patients (31%) experienced an AE leading to permanent discontinuation of study treatment, including agitation, cerebrovascular accident, ejection fraction decreased, and Pneumocystis jirovecii pneumonia. No patients in any other cohorts had permanent discontinuation for an AE.

AEs led to dose interruption or delay in 75–92% of patients across cohorts and dose reduction in 50–75% of patients.

- Dose reduction or interruption/delay was attributed to keratopathy in 4 (33%) patients in the 1.9 mg/kg Q8W cohort, and 69–85% of patients in the other cohorts.

Fatal SAEs were reported in 3 patients:

- One patient in the 2.5 mg/kg Q4W (split) cohort had Pneumocystis jirovecii pneumonia considered unrelated to treatment.
- Two patients in the 2.5 mg/kg Q4W cohort had fatal SAEs, one pneumonia, and one a combination of pneumonia, sepsis, and febrile neutropenia; febrile neutropenia was considered related to belamaf and Len treatment.

Table 3. Safety data and duration of follow-up for patients treated with belamaf + Len/Dex across cohorts

Outcome, n (%)	Belamaf 1.9 mg/kg Q8W + Len/Dex, n=12	Belamaf 1.9 mg/kg Q4W + Len/Dex, n=4	Belamaf 2.5 mg/kg Q4W + Len/Dex, n=16	Belamaf 2.5 mg/kg Q4W (split) + Len/Dex, n=13
Any AE	12 (100)	4 (100)	16 (100)	13 (100)
AEs related to				
Belamaf	9 (75)	4 (100)	15 (94)	13 (100)
Len	7 (58)	4(100)	12 (75)	7 (54)
Dex	10 (83)	2 (50)	11 (69)	8 (62)
AE related to any study treatment*	11 (92)	4 (100)	15 (94)	13 (100)
Grade 3 or 4 AEs	8 (67)	2 (50)	13 (81)	12 (92)
Belamaf	4 (33)	2 (50)	12 (75)	8 (62)
Len	4 (33)	2 (50)	9 (56)	6 (46)
Dex	2 (17)	0	7 (44)	4 (31)
Grade 3 or 4 AEs related to any study treatment	5 (42)	2 (50)	13 (81)	11 (85)
Grade ≥3 AEs occurring at ≥25% in at least 1 cohort				
Keratopathy	0	1 (25)	8 (50)	6 (46)
Platelet count decreased	2 (17)	0	4 (25)	5 (38)
Visual acuity reduced	1 (8)	1 (25)	5 (31)	3 (23)
Neutrophil count decreased	2 (17)	1 (25)	3 (19)	2 (15)
Neutropenia	0	1 (25)	1 (6)	3 (23)
Thrombocytopenia	0	1 (25)	2 (13)	0
Diarrhea	0	1 (25)	0	1 (8)
AEs leading to permanent discontinuation of study treatment	0	0	0	4 (31)
AEs leading to dose reduction	6 (50)	3 (75)	12 (75)	9 (69)
AEs leading to dose interruption/delay	11 (92)	3 (75)	13 (81)	12 (92)
Most common AEs leading to dose reduction/interruption/delay				
Keratopathy	4 (33)	3 (75)	11 (69)	11 (85)
Visual acuity reduced	3 (25)	1 (25)	5 (31)	2 (15)
Platelet count decreased	2 (17)	0	3 (19)	3 (23)
Neutrophil count decreased	2 (17)	1 (25)	2 (13)	1 (8)
Insomnia	2 (17)	2 (50)	0	1 (8)
Neutropenia	0	1 (25)	1 (6)	3 (23)
Thrombocytopenia	0	1 (25)	3 (19)	1 (8)
Any SAE	5 (42)	2 (50)	9 (56)	6 (46)
Treatment-related SAE	2 (17)	0	3 (19)	3 (23)
Fatal SAE	0	0	2 (13)†	1 (8)

*Affirmative or missing response to the query "Is there a reasonable possibility that the AE may have been caused by study treatment?"; †Fatal SAE considered treatment-related in 1 patient, attributed to both belamaf and Len.

Ocular events

Ocular events included corneal exam findings, such as keratopathy, and ocular symptoms, such as blurred vision and changes in best corrected visual acuity (BCVA).

- There were no clear trends in BCVA changes among cohorts, in part limited by small sample size.
- Blurred vision of grade 2 or 3 was more common in the 2.5 mg/kg cohorts than in the 1.9 mg/kg cohorts.

Table 4. Ocular events observed in patients treated with belamaf + Len/Dex across cohorts

Outcome, n (%)	Belamaf 1.9 mg/kg Q8W + Len/Dex, n=12	Belamaf 1.9 mg/kg Q4W + Len/Dex, n=4	Belamaf 2.5 mg/kg Q4W + Len/Dex, n=16	Belamaf 2.5 mg/kg Q4W (split) + Len/Dex, n=13
Worst case post-baseline change in BCVA				
≤2 line decline (better eye)	8 (67)	3 (75)	12 (75)	9 (69)
≥3 line decline (better eye)	1 (8)	1 (25)	2 (13)	3 (23)
≤2 line decline (worse eye)	6 (50)	3 (75)	7 (44)	5 (38)
≥3 line decline (worse eye)	3 (25)	1 (25)	7 (44)	7 (54)
Keratopathy*				
Grade 1	2 (17)	1 (25)	0	2 (15)
Grade 2	7 (58)	1 (25)	3 (19)	4 (31)
Grade 3	0	1 (25)	8 (50)	6 (46)
Grade 4	0	0	0	0
Blurred vision†				
Grade 1	2 (17)	0	2 (13)	1 (8)
Grade 2	2 (17)	1 (25)	2 (13)	4 (31)
Grade 3	1 (8)	1 (25)	6 (38)	4 (31)
Grade 4	0	0	0	0

*Keratopathy is a corneal exam finding. †Blurred vision includes visual symptoms such as changes to BCVA and blurry vision.

Pharmacokinetics

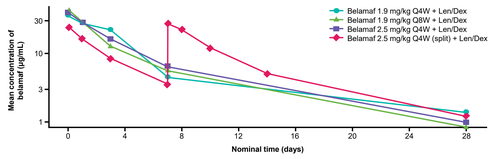
The PK of belamaf was explored in all cohorts (**Figure 3**).

Lower peak and higher trough belamaf concentrations were observed with the split dosing schedule.

Belamaf PK profile was similar to that previously observed in patients with RRMM, taking into consideration baseline patient characteristics.[9]

Lenalidomide PK were as anticipated, confirming lack of drug–drug interaction with belamaf.

Figure 3. Mean concentration–time profile of belamaf



Conclusions

Belamaf + Len/Dex demonstrated a tolerable safety profile, with no new safety signals identified.

Encouraging clinical activity, albeit in small sample sizes, is observed with this combination in patients with RRMM.

- Belamaf + Len/Dex demonstrated clinical activity, with the highest ORR reported in the 1.9 mg/kg Q4W and 2.5 mg/kg Q4W (split) cohorts (75% and 69%, respectively).
- In addition, the 2.5 mg/kg Q4W cohort reported an ORR of 63% (10 out of 16). Of those with an ORR, 80% (8 out of 10) demonstrated a deeper response (≥VGPR).
- mDOR was not reached in any of the cohorts except the 1.9 mg/kg Q4W cohort (11.1 months).
- mPFS was reached in the 1.9 mg/kg Q4W and 2.5 mg/kg Q4W (split) cohorts.

Belamaf PK profile was similar to that observed in patients with RRMM, taking into consideration baseline patient characteristics, and there was no PK interaction between lenalidomide and belamaf.

Belamaf has been found to induce deep and durable responses over time, as demonstrated in the DREAMM-2 study.[6,7] Therefore, it is hypothesized that ORR in this study will increase across all cohorts with prolonged exposure.

Further studies are ongoing to better understand the clinical benefit and safety of combining belamaf with Len/Dex in patients with RRMM.

Abbreviations

ADA, anti-drug antibodies; AEs, adverse events; BCMA, B-cell maturation antigen; belamaf, belantamab mafodotin; BCVA, best corrected visual acuity; CBR, clinical benefit rate (DMR); CI, confidence interval; CRR, complete response rate; Dex, dexamethasone; DLT, dose-limiting toxicity; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; FLC, free light chain; Ig, immunoglobulin; IMWG, International Myeloma Working Group; ISS, International Staging System; Len, lenalidomide; LOT, line of therapy; mAb, monoclonal antibody; MM, multiple myeloma; MMAF, monomethyl auristatin F; MR, moderate response; NEI-VFQ-25, National Eye Institute Visual Function Questionnaire; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reached; ORR, overall response rate; OSDI, Ocular Symptom Disease Index; PD, progressive disease; PK, pharmacokinetics; PO, by mouth; PR, partial response; PRO, patient-reported outcomes; RRMM, relapsed/refractory multiple myeloma; Q3W, every 3 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; SAE, serious adverse event; sCR, stringent complete response; SD, stable disease; SFLC, serum FLC; VGPR, very good partial response.

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