Characterisation and Management of Ocular Events in Patients Treated with Belamaf, Bortezomib and Dexamethasone: DREAMM-7

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Belamaf dose modifications helped manage ocular events through an individualised dosing schedule based on patient tolerability

Introduction

The use of triplet and quadruplet regimens is increasing in patients with newly diagnosed multiple myeloma, leading to earlier exposure to major drug classes and a need for combinations incorporating different mechanisms of action (MOAs) at first relapse[1-3]

Belantamab mafodotin (belamaf) is a humanised, afucosylated anti-B-cell maturation antigen (BCMA) monoclonal antibody that is conjugated to the microtubule inhibitor monomethyl auristatin F (MMAF) by a protease-resistant cysteine linker; it acts through a multimodal mechanism, including direct cell killing and immune-mediated mechanisms[4-6]

In the phase 3 DREAMM-7 (NCT04246047) trial, treatment with belamaf, bortezomib and dexamethasone (BVd) led to a statistically significant progression-free survival (PFS) benefit (hazard ratio [HR] 95% confidence interval [CI], 0.41 [0.31–0.53]; P<.00001). Median overall survival (OS) was not reached in either arm. BVd demonstrated a statistically significant OS benefit vs daratumumab, bortezomib and dexamethasone (DVd) (HR [95% CI], 0.58 [0.43-0.79]) in patients with relapsed/refractory multiple myeloma after ≥1 prior line of therapy[7]

Belamaf is associated with a risk of ocular events, which are thought to be associated with the MMAF payload and were managed through dose modifications, including discontinuation in 9% of patients[7,8]

Methods

- In DREAMM-7, eligible patients were randomised 1:1 to receive BVd or DVd; belamaf was given at a dose of 2.5 mg/kg every 3 weeks (Q3W) **(Figure 1)**
- In addition to ocular adverse reactions (ARs) ophthalmic exam findings were evaluated using the Keratopathy and Visual Acuity (KVA) scale and drove dose modifications **(Figure 1)**
- Ocular ARs graded by Common Terminology Criteria for Adverse Events (CTCAE) and ophthalmic exam findings (including corneal exam findings and changes in best-corrected visual acuity [BCVA]) assessed by KVA are summarised using descriptive statistics

Figure 1: **DREAMM-7 study design and dosing algorithm**

DVd	BVd
Daratumumab 16 mg/kg IV cycles 1-3 QW and cycles 4-8 Q3W **+ bortezomib + dexamethasone**[a] cycles 1-8	**Belamaf** 2.5 mg/kg IV Q3W **+ bortezomib + dexamethasone**[a] cycles 1-8
Daratumumab monotherapy 16 mg/kg IV Q4W cycle 9+	**Belamaf monotherapy** 2.5 mg/kg IV Q3W cycle 9+

Stratification
- Prior lines of treatment (1 vs 2 or 3 vs ≥4)
- Prior bortezomib (yes vs no)
- Prior anti-CD38 therapy (yes vs no)

Median duration of follow-up (ITT): 28.24 months (range, 0.10–40.02 months). Data cutoff: 2 October 2023

Standard belamaf dose and schedule 2.5 mg/kg administered Q3W[b]

No ophthalmic exam finding → **Continue standard schedule**

Grade 2 ophthalmic exam finding
- ***Corneal exam findings:*** moderate SPK; patchy microcyst-like deposits; subepithelial haze and stromal opacity
  and/or
- ***Change in BCVA:*** decline of 2 or 3 lines on Snellen exam from baseline

→ **Dose delay** until improvement to KVA grade ≤1[c,d] **then resume standard dose of** 2.5 mg/kg Q3W

Grade 3 ophthalmic exam finding
- ***Corneal exam findings:*** severe SPK; diffuse microcyst-like deposits; subepithelial haze and stromal opacity
  and/or
- ***Change in BCVA:*** decline of >3 lines on Snellen exam from baseline

→ **Dose delay** until improvement to KVA grade ≤1[c,d] **then resume at reduced dose of** 1.9 mg/kg Q3W[e]

Grade 4 ophthalmic exam finding
- ***Corneal exam findings:*** corneal epithelial defect
  and/or
- ***Change in BCVA:*** Snellen equivalent visual acuity worse than 20/200

→ **Permanently discontinue** belamaf
Patient may undergo **rechallenge at a reduced dose** after improvement and following sponsor approval[f]

BCVA, best-corrected visual acuity; belamaf, belantamab mafodotin; BVd, belamaf, bortezomib and dexamethasone; CD, cluster of differentiation; DVd, daratumumab, bortezomib and dexamethasone; IV, intravenous; KVA, Keratopathy and Visual Acuity; Q3W, every 3 weeks; Q4W, every 4 weeks; QW, once weekly; SC, subcutaneous; SPK, superficial punctate keratitis.

[a] *Bortezomib 1.3 mg/m² SC administered on days 1, 4, 8 and 11 of cycles 1 to 8 (21-day cycles) and dexamethasone 20 mg administered on the day of and day after bortezomib in cycles 1 to 8. Reduce starting dose of dexamethasone to 10 mg for patients aged ≥75 years who have a body mass index of <18.5 kg/m², previous unacceptable adverse reactions associated with glucocorticoid therapy or inability to tolerate the starting dose.* [b] *Dose modifications should be based on the most severe grade. If eyes differ in severity, dose modification guideline should be applied based on the more severe eye.* [c] *A grade 1 KVA event defined by corneal exam finding is a mild SPK (documented worsening from baseline) with or without symptoms and by change in BCVA is a decline from baseline of 1 line on Snellen visual acuity.* [d] *Improvement in either corneal exam findings or changes in BCVA to grade ≥1.* [e] *If already on reduced (1.9 mg/kg) dose, patient should resume treatment at that dose level. Consider re-escalating after ≥2 ophthalmic assessments post treatment reinitiation for events that do not worsen after resuming at a lower dose and following benefit-risk assessment and discussion with the sponsor.* [f] *Patient may undergo rechallenge on a case-by-case basis at a reduced dose after improvement and following benefit-risk assessment and discussion between the eye care specialist, investigator and sponsor.*

Results

- Ocular ARs were more frequent in the BVd arm than the DVd arm **(Table 1)**; however, global quality of life (QOL) was not different between arms over time, as measured by the EORTC Core Quality of Life questionnaire (EORTC QLQ-C30)[9] (Hungria V, et al. EHA 2024. Poster P945)

Ocular events were managed by dose modifications that extended dosing intervals

- Among all patients who received BVd, 44% had dose reductions, 78% had dose delays/interruptions and 9% discontinued due to ocular events assessed by CTCAE and KVA. Median (range) doses of belamaf received before discontinuation due to ocular events was 5 (2-37)
- Administration of the 2.5-mg/kg dose decreased, while administration of the 1.9-mg/kg dose increased; time between doses increased at later time periods **(Table 2)**

Table 1: **Summary of common ocular ARs**

Ocular AR of special interest (by CTCAE) preferred terms, n (%)[a,b]	BVd (N=242)		DVd (N=246)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
≥30% of patients in either treatment group				
Any event	191 (79)	82 (34)	72 (29)	7 (3)
Vision blurred	160 (66)	53 (22)	26 (11)	2 (1)
Dry eye	123 (51)	17 (7)	17 (7)	0
Photophobia	114 (47)	5 (2)	6 (2)	0
Foreign body sensation in eye	106 (44)	8 (3)	10 (4)	0
Eye irritation	103 (43)	12 (5)	13 (5)	0
Eye pain	77 (32)	2 (1)	8 (3)	1 (<1)

AR, adverse reaction; BVd, belamaf, bortezomib and dexamethasone; CTCAE, Common Terminology Criteria for Adverse Events; DVd, daratumumab, bortezomib and dexamethasone; eCRF, electronic case report form.

[a] *Ocular ARs assessed by CTCAE grade were based on a hybrid of 172 terms identified in the eCRF and GSK internal review.* [b] *Ocular exams for patients in the BVd arm were assessed at screening/baseline and then every 3 weeks prior to dosing up to at least the 6th dose of belamaf and then every 3 months if no significant ocular findings were observed. For patients in the DVd arm, ocular exams were performed at screening/baseline with on-treatment ocular exams performed at cycle 6 and then every 6 months.*

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Table 2: **Dose exposure of belamaf[a,b]**

		0 to ≤6 months (n=242)	>6 to ≤12 months (n=162)	>12 months (n=132)	Overall (N=242)
No. of infusions per patient	Mean	4.35	3.75	8.9	11.7
	Median (IQR)	4 (3-6)	3 (2-6)	6.5 (4-13)	9 (4-16)
Total no. of doses		1133	577	1122	2832
Doses administered by dose level	2.5 mg/kg, n (%)	768 (68)	198 (34)	201 (18)	1167 (41)
	1.9 mg/kg, n (%)	365 (32)	379 (66)	921 (82)	1665 (59)
Time between doses per patient[c]	n	231	130	124	231
	Mean, weeks	4.78	6.80	10.91	7.21
	Median (IQR), weeks	3.6 (3-6)	4.7 (3-8)	9.5 (5-15)	5.7 (3-10)

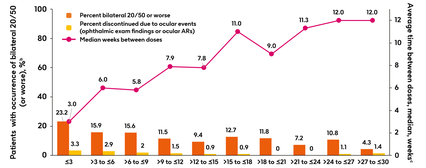
belamaf, belantamab mafodotin; IQR, interquartile range.

[a] *Post hoc analysis.* [b] *Intervals for 0 to ≤6 months, >6 to ≤12 months and >12 months were calculated either by using days or days converted to months.* [c] *The statistics for time between doses only considered patients who had >1 visit during their treatment period.*

Belamaf dose modifications helped improve BCVA worsening

- Visual acuity changes are important to patients because they can affect activities of daily living; however, worsening of visual acuity can be improved by belamaf dose modifications
  - Previously, we have shown that 34% with normal baseline (20/25 or better in ≥1 eye) had worsening of BCVA to bilateral 20/50 or worse; of these patients, 98% had improvement, and 94% had resolution to normal baseline (20/25 or better in ≥1 eye) of their first event by data cutoff[7]
- Median time between doses increased over time due to dose delays; 23% (N=49/211) of patients experienced 20/50 or worse events in the first 3 months **(Figure 2)**
- **Figure 3** demonstrates the prevalence of ocular ARs by time on treatment

Figure 2: **Prevalence of bilateral BCVA 20/50 or worse and time interval between doses by time on treatment[a]**



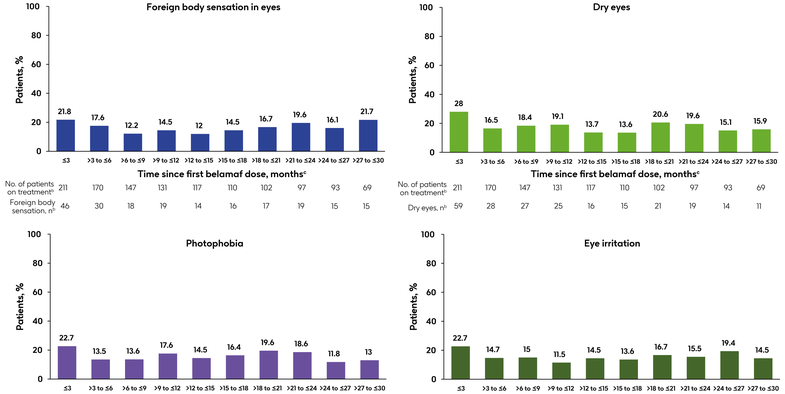
	≤3	>3 to ≤6	>6 to ≤9	>9 to ≤12	>12 to ≤15	>15 to ≤18	>18 to ≤21	>21 to ≤24	>24 to ≤27	>27 to ≤30
No. of patients on treatment[b]	211	170	147	131	117	110	102	97	93	69
No. of patients with bilateral 20/50 or worse[b]	49	27	23	15	11	14	12	7	10	3
Median days between doses[b]	21	42	41	55	54	77	63	79	84	84
No. of patients who discontinued due to KVA or ocular CTCAE event[b]	7	5	3	2	1	1	0	0	1	1

AR, adverse reaction; BCVA, best-corrected visual acuity; belamaf, belantamab mafodotin.

[a] *Only the belamaf treatment period was considered in these post hoc analyses.* [b] *Only patients with 20/25 or better in ≥1 eye at baseline are considered.* [c] *Mean of days between doses for each patient per interval is used.* [d] *Graph is truncated at 30 months because data beyond 30 months represented low number of patients on treatment (>30 to ≤33 months, n=42; >33 to ≤36 months, n=20; >36 to ≤39 months, n=8; >39 to ≤42 months, n=3).*

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Figure 3: **Prevalence of ocular ARs by time on treatment[a]**



	≤3	>3 to ≤6	>6 to ≤9	>9 to ≤12	>12 to ≤15	>15 to ≤18	>18 to ≤21	>21 to ≤24	>24 to ≤27	>27 to ≤30
No. of patients on treatment[b]	211	170	147	131	117	110	102	97	93	69
Foreign body sensation, n[b]	46	30	18	19	14	16	17	19	15	15
Dry eyes, n[b]	59	28	27	25	16	15	21	19	14	11
Photophobia, n[b]	48	23	20	23	17	18	20	18	11	9
Eye irritation, n[b]	48	25	22	15	17	15	17	15	18	10

AR, adverse reaction; belamaf, belantamab mafodotin.

[a] *Only the belamaf treatment period was considered in these post hoc analyses.* [b] *Only patients with 20/25 or better in ≥1 eye at baseline are considered.* [c] *Graphs are truncated at 30 months because data beyond 30 months represented low number of patients on treatment (>30 to ≤33 months, n=42; >33 to ≤36 months, n=20; >36 to ≤39 months, n=8; >39 to ≤42 months, n=3).*

Despite dose modifications, treatment efficacy was maintained

- In patients who had ≥1 grade ≥2 ophthalmic exam finding **(Table 3)**:
  - 91% continued belamaf following the first event and received a median of 8 belamaf infusions following the first event; 93% achieved ≥ partial response (PR), and 75% achieved ≥ very good partial response (VGPR)
- Median PFS in patients with dose delays of ≥12 weeks was 36.6 months **(Table 4)**
- The majority of patients (89%) had ≥ PR before their first extended (>6 weeks) dose delay
  - 95% (63/66) of patients with ≥ VGPR experiencing an extended dose delay maintained or deepened their response (ie, ≥ VGPR) **(Table 5)**
  - 95% (35/37) of patients with ≤ PR who received 1 to 2 doses reached, maintained or deepened their response (ie, ≥ PR) after their first dose delay
- 97% (194/201) of patients in the BVd arm who had a response had ≥1 dose delay, with a median dose delay lasting 57 days (IQR, 18-88 days). Overall, 88% (213/242) of patients in the BVd arm had ≥1 dose delay, with a median dose delay lasting 54 days (interquartile range [IQR], 18-88 days)

Table 3: **Best response in patients who had grade ≥2 ophthalmic exam finding[a]**

Patients with ≥1 grade ≥2 ophthalmic exam finding	**BVd**
Experienced ≥1 event (grade ≥2), n/N (%)	209/242 (86)
Continued belamaf following the onset of first event, n/N (%)	190/209 (91)
No. of additional doses after event, median (range)	8 (1-52)
Best response, n/N (%)[b]	
ORR (≥ PR)	177/190 (93)
≥ VGPR	143/190 (75)

belamaf, belantamab mafodotin; BVd, belamaf, bortezomib and dexamethasone; KVA, Keratopathy and Visual Acuity; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

[a] *Post hoc analysis.* [b] *Reflects best response at any time on treatment and not only following the first KVA event.*

Table 4: **PFS in patients with extended belamaf dose delay (≥12 weeks)[a]**

Patients with ≥6 months of treatment[b]	**BVd (n=242)**
No. of patients with ≥1 dose delay of ≥12 weeks	126
PFS, median (95% CI), months	36.6 (33.2-NR)

belamaf, belantamab mafodotin; BVd, belamaf, bortezomib and dexamethasone; CI, confidence interval; NR, not reached; PD, progressive disease; PFS, progression-free survival.

[a] *Post hoc analysis.* [b] *Only patients receiving ≥6 months of treatment were included in the analysis to exclude early discontinuations (eg, rapid PD).*

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Conclusions

Dose modifications helped manage ocular events through an individualised dosing schedule based on patient tolerability
- Dose modifications resulted in extended dosing intervals for belamaf at later time periods
- Median time between doses increased over time due to dose delays
- 23% (N=49/211) of patients experienced 20/50 or worse events in the first 3 months

Efficacy was maintained in the majority of patients requiring extended belamaf dose delays
- The majority of patients maintained or deepened their response following the first extended dose delay (≥2 cycles), including those who had a dose hold after 1 or 2 doses of belamaf
  - 95% of patients with ≤ PR who received 1 to 2 doses reached, maintained or deepened their response after their first dose delay
- Median PFS was 36.6 months in patients requiring extended belamaf dose delay (≥12 weeks)

Results

Table 5: **Best response before and during/after the first extended dose delay of ≥2 cycles of belamaf[a,b]**

First extended dose delay at any time (N=146)

Best response before the first dose delay[c]		**Best response during/after the first dose delay**	
Response	n (%)	**Response**	n/n (%)
≤ PR[d]	80 (55)	**≥ VGPR**	46/80 (58)
		≥ PR	75/80 (94)
≥ VGPR	66 (45)	**sCR/CR**	36/66 (55)
		≥ VGPR	63/66 (95)

95% with ≥ VGPR before extended dose delay maintained or deepened their response

First extended dose delay following 1 to 2 doses (N=48)

Best response before the first dose delay[c]		**Best response during/after the first dose delay**	
Response	**n (%)**	**Response**	**n/n (%)**
≤ PR[d]	37 (77)	**≥ VGPR**	28/37 (76)
		≥ PR	35/37 (95)
≥ VGPR	11 (23)	**sCR/CR**	7/11 (64)
		≥ VGPR	10/11 (91)

95% with ≤ PR before extended dose delay reached, maintained or deepened their response

belamaf, belantamab mafodotin; CR, complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

[a] *Post hoc analysis.* [b] *Dose delays are derived when the time between belamaf dose administration or the time from last dose to death, decision to discontinue treatment, treatment discontinuation date, start of new anti-myeloma therapy or last contact date is ≥31 days.* [c] *Dose delay was ≥6 weeks (ie, ≥2 cycles).* [d] *Includes 2 patients who had non-evaluable responses.*

Abbreviations

AR, adverse reaction; BCMA, B-cell maturation antigen; BCVA, best-corrected visual acuity; belamaf, belantamab mafodotin; BVd, belamaf, bortezomib and dexamethasone; CD, cluster of differentiation; CI, confidence interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DVd, daratumumab, bortezomib and dexamethasone; eCRF, electronic case report form; EORTC QLQ-C30, EORTC Core Quality of Life questionnaire; HR, hazard ratio; IQR, interquartile range; IV, intravenous; KVA, Keratopathy and Visual Acuity; MMAF, monomethyl auristatin F; MOA, mechanism of action; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; Q4W, every 4 weeks; QOL, quality of life; QW, once weekly; SC, subcutaneous; sCR, stringent complete response; SPK, superficial punctate keratitis; VGPR, very good partial response.

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Jessica Best has been added as an author and will present on behalf of the original authors for this encore poster with their permission.

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