Characterisation and Management of Ocular Events in Patients Treated with Belamaf, Pomalidomide and Dexamethasone: DREAMM-8

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

Introduction

Triplet and quad therapies incorporating proteasome inhibitors (PIs), immunomodulatory drugs and anti-CD38 antibodies are the standard of care (SOC) in newly diagnosed multiple myeloma (NDMM), leading to an increased number of patients exposed/refractory to these agents at first relapse[1-4]

- Therefore, combinations that incorporate different mechanisms of action (MOAs) for patients with relapsed/refractory multiple myeloma (RRMM) at first and subsequent relapses are needed[1-3]

Belantamab mafodotin (belamaf) is a humanised, afucosylated, anti-B-cell maturation antigen (BCMA) monoclonal antibody 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]

The global, phase 3, open-label, randomised DREAMM-8 trial (NCT04484623) investigated belamaf, pomalidomide and dexamethasone (BPd) vs pomalidomide, bortezomib and dexamethasone (PVd) in patients with RRMM who had received ≥1 prior line of therapy, including lenalidomide **(Table 1)**[7]

- In DREAMM-8, BPd led to a statistically significant reduction in the risk of disease progression or death vs PVd
- Progression-free survival (PFS) benefit was complemented by the other efficacy endpoints tested
- Ocular reactions were the most commonly reported adverse reactions (ARs) and were managed by dose modifications

In these descriptive analyses, we describe the management of belamaf-related ocular events in DREAMM-8

Table 1: **Summary of efficacy endpoints**[7]

Endpoint	ITT population	
	BPd (N=155)	PVd (N=147)
PFS, median (95% CI), months	NR (20.6-NR)	12.7 (9.1-18.5)
HR (95% CI); *P* value[a]	0.52 (0.37-0.73); <.001	
OS, median (95% CI), months	NR (33.0-NR)	NR (25.2-NR)
HR (95% CI)	0.77 (0.53-1.14)	
ORR (sCR + CR + VGPR + PR), n (%) [95% CI]	120 (77) [70.0-83.7]	106 (72) [64.1-79.2]
CR or better (sCR + CR), n (%) [95% CI]	62 (40) [32.2-48.2]	24 (16) [10.7-23.3]
MRD negativity rate (patients with CR or sCR)	37 (23.9)	7 (4.8)
n (%) [95% CI]	[17.4-31.4]	[1.9-9.6]
DOR, median (95% CI), months[a]	NR (24.9-NR)	17.5 (12.1-26.4)
PFS2, median (95% CI), months	NR (33.0-NR)	22.4 (13.8-NR)

BPd, belamaf, pomalidomide and dexamethasone; CI, confidence interval; CR, complete response; DOR, duration of response; HR, hazard ratio; ITT, intent to treat; MRD, minimal residual disease; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PVd, pomalidomide, bortezomib and dexamethasone; sCR, stringent complete response; VGPR, very good partial response.

[a] The treatment effect (HR and corresponding 95% CI) was estimated using the stratified Cox proportional hazards model, and the P-value was produced based on the 1-sided stratified log-rank test. Stratified analyses were adjusted for the number of prior lines of therapy and prior bortezomib use. [b] CIs estimated using the Brookmeyer-Crowley method.

Methods

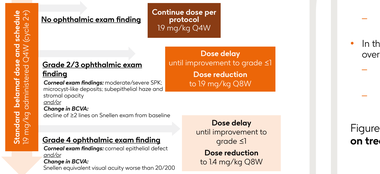
- In DREAMM-8, eligible patients were randomised 1:1 to receive BPd or PVd **(Figure 1)**
  - The starting dose of belamaf was 2.5 mg/kg intravenous (IV) (cycle 1 day 1) followed by 1.9 mg/kg every 4 weeks (Q4W) (cycle 2 and onward)
- In addition to ocular ARs, ophthalmic examination findings were evaluated using the Keratopathy and Visual Acuity (KVA) scale and drove dose modifications **(Figures 1 and 2)**
- Ocular ARs graded by Common Terminology Criteria for Adverse Events (CTCAE) and ophthalmic examination findings (including corneal exam findings and changes in best-corrected visual acuity [BCVA]) graded by KVA are summarised using descriptive statistics

Figure 1: **DREAMM-8 study design and dosing algorithm**

PVd	BPd
Bortezomib 1.3 mg/m² SC on days 1, 4, 8 and 11 of cycles 1-8 then days 1 and 8 (21-day cycles) + **pomalidomide** 4 mg orally on days 1-14 (21-day cycles) + **dexamethasone** 20 mg[a] on the day of and day after bortezomib	**Belantamab mafodotin** 2.5 mg/kg IV (cycle 1) then 1.9 mg/kg IV Q4W from cycle 2 onward + **pomalidomide** 4 mg orally on days 1-21 (28-day cycles) + **dexamethasone** 40 mg[a] on days 1, 8, 15 and 22

Stratification[b]
- 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): 21.78 months (range, 0.03-39.23 months). Data cutoff: 29 January 2024



BCVA, best-corrected visual acuity; belamaf, belantamab mafodotin; BPd, belamaf, pomalidomide and dexamethasone; CD, cluster of differentiation; ISS, International Staging System; ITT, intent to treat; IV, intravenous; PVd, pomalidomide, bortezomib and dexamethasone; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SPK, superficial punctate keratitis.

[a] Patients aged ≥75 years who had comorbidities or were intolerant of the 40-mg dose in arm A or 20-mg dose in arm B could have dose level reduced to half, per investigator discretion. [b] Some patients were stratified by ISS stage (1 vs II/III); the protocol was amended on 20 April 2021 to replace this randomisation factor with prior anti-CD38 treatment (yes vs no).

Figure 2: **Evaluation of ocular events**

Ocular ARs
- Ocular adverse event of special interest
- Graded per CTCAE version 5
- Include mainly ocular symptoms reported by patients[a]

Ophthalmic exam findings
- Include:
  - Changes in BCVA
  - Corneal slit lamp exam findings
- Graded per the KVA scale

AR, adverse reaction; BCVA, best-corrected visual acuity; CTCAE, Common Terminology Criteria for Adverse Events; KVA, Keratopathy and Visual Acuity

[a] Examination findings were reported as ARs prior to implementation of the KVA scale.

Results

- At data cutoff (29 January 2024), 150 patients in the BPd arm and 145 patients in the PVd arm had received ≥1 dose of study treatment

The ocular safety profile was generally consistent with the known safety profile of belamaf

- The majority of patients (89%) treated with BPd experienced an ocular event; 89% reported an ocular AR **(Table 2)**, while grade ≥2 ophthalmic exam findings were reported in 82%
- The median time between belamaf doses increased with longer time on treatment **(Table 3)**

Table 2: **Most commonly reported ocular ARs (≥30% of patients in either treatment group)**

Ocular ARs of special interest (by CTCAE) preferred terms, n (%)[a]	BPd (N=150)		PVd (N=145)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any event	133 (89)	65 (43)	44 (30)	3 (2)
Vision blurred	119 (79)	26 (17)	22 (15)	0
Dry eye	91 (61)	12 (8)	14 (10)	0
Foreign body sensation in eye	91 (61)	9 (6)	9 (6)	0
Eye irritation	75 (50)	6 (4)	13 (9)	0
Photophobia	66 (44)	5 (3)	6 (4)	0
Eye pain	49 (33)	3 (2)	7 (5)	0

AR, adverse reaction; belamaf, belantamab mafodotin; BPd, belamaf, pomalidomide and dexamethasone; CTCAE, Common Terminology Criteria for Adverse Events; eCRF, electronic case report form; PVd, pomalidomide, bortezomib and dexamethasone.

[a] Ocular ARs assessed by CTCAE grade were based on a hybrid of 172 terms identified in the eCRF and GSK internal review. From Dimopoulos M, et al. N Engl J Med. 2024. doi: 10.1056/NEJMoa2403407. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Table 3: **Dose exposure of belamaf**[a,b]

		0 to ≤6 mo (n=150)	>6 to ≤12 mo (n=104)	>12 mo (n=77)	Overall (N=150)
No. of infusions per patient	Mean	3.8	2.3	3.7	7.3
	Median (IQR)	4 (3-5)	2 (1-3)	3 (1-5)	6 (4-10)
Total no. of doses		570	242	286	1098
Doses administered by dose level, n (%)	2.5 mg/kg	151 (26)	–	–	151 (14)
	1.9 mg/kg	415 (73)	235 (97)	267 (93)	917 (84)
	1.4 mg/kg	4 (<1)	7 (3)	19 (7)	30 (3)
Time between doses per patient[c]	N	129	79	77	142
	Mean, wk	5.26	11.91	14.2	9.46
	Median (IQR), wk	4.1 (4-5)	11.8 (5-16)	14.1 (10-18)	8.7 (5-13)

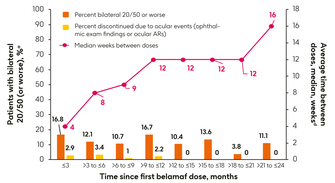
belamaf, belantamab mafodotin; IQR, interquartile range.

[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 manage ocular events

- Dose modifications resulted in extended belamaf dosing intervals
  - 93% of patients experienced ≥1 dose delay; 62% experienced ≥3 dose delays
  - Reduction in dosing frequency from Q4W to Q8W occurred in 58% of patients
- In the BPd group, the following trends were observed over time on treatment:
  - The median interval between belamaf doses increased (**Table 3** and **Figure 3**)
  - 16.8% of patients experienced BCVA 20/50 or worse in the first 3 months of treatment (**Figure 3**)
  - **Figure 4** demonstrates the prevalence of ocular ARs by time period on treatment
- Discontinuations due to ocular events occurred in 9% of patients **(Figure 3)**
- At data cutoff, ocular events had resolved as follows:
  - The first occurrence of ophthalmic exam finding returned to baseline level in 89% of patients
  - The first occurrence of bilateral BCVA 20/50 or worse returned to baseline level in 84% of patients
  - The event returned to baseline level in all 14 patients (9%) who discontinued belamaf due to an ocular event

Figure 3: **Prevalence of bilateral BCVA 20/50 or worse and time interval between doses by time period on treatment**[a,b]

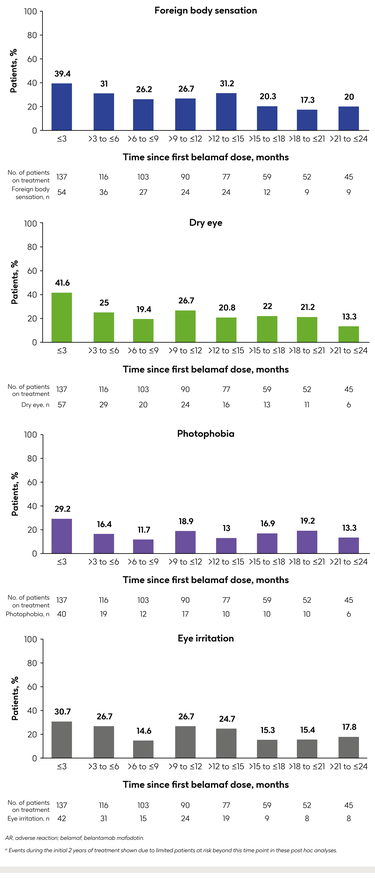


No. of patients on treatment, n[c]	137	116	103	90	77	59	52	45
No. of patients with bilateral 20/50 or worse, n[c]	23	14	11	15	8	8	2	5
Median days between doses[c]	28.5	56	63.5	84	84	86	84	111
No. of patients who discontinued due to ocular event, n[c]	4	4	1	2	0	0	0	0

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] First 2 years of treatment shown due to limited patients at risk beyond this time point. [c] Only patients with 20/25 or better in either or both eyes at baseline are considered. [d] Mean of days between doses for each patient per interval is used. Dimopoulos MA, et al. Presented at the European Haematology Association (EHA) 28th Annual Meeting 2024. Oral presentation LBA2. Reprinted with permission by the author.

Figure 4: **Prevalence of ocular ARs by time period 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
Foreign body sensation	39.4	31	26.2	26.7	31.2	20.3	17.3	20
Dry eye	41.6	25	19.4	26.7	20.8	22	21.2	13.3
Photophobia	29.2	16.4	11.7	18.9	13	16.9	19.2	13.3
Eye irritation	30.7	26.7	14.6	26.7	24.7	15.3	15.4	17.8

AR, adverse reaction; belamaf, belantamab mafodotin.

[a] Events during the initial 2 years of treatment shown due to limited patients at risk beyond this time point in these post hoc analyses.

Efficacy was maintained in the majority of patients with belamaf dose modifications

- Most responders in the BPd group had belamaf dose modifications leading to extended dose intervals **(Table 4)**
  - 99% had ≥1 dose delay lasting a median of 53 days (interquartile range [IQR], 25-83 days)
  - 74% required ≥3 dose delays
  - 70% had dose reduction from a Q4W regimen to an every 8 weeks (Q8W) regimen
- Among patients who had ≥1 grade ≥2 ophthalmic exam finding **(Table 5)**:
  - 98% were able to resume belamaf and received a median of 5 belamaf infusions following the first event
  - 88% achieved a best response of ≥ partial response (PR), and 75% achieved ≥ very good partial response (VGPR)
- Among patients who had ≥1 belamaf dose delay of >8 weeks **(Table 6)**:
  - 87% had achieved a response (≥ PR) prior to the delay
  - Of those who had not achieved adequate response (≤ PR) prior to the first dose delay, 92% eventually achieved a best response of ≥ PR, and 73% achieved ≥ VGPR
  - 98% of those with ≥ VGPR prior to the first dose delay maintained or deepened their response during or following the delay
- 13 patients required belamaf dose delay >8 weeks early (after ≤2 doses)
  - 8 had achieved a response (≥ PR) prior to the dose delay; after which responses deepened in 7 of 8 patients
  - All 5 patients who had not achieved a response prior to the dose delay achieved a response during or following it
- Median PFS was not reached in patients who received ≥6 months of treatment and required ≥1 dose delay ≥12 weeks **(Table 7)**

Table 4: **Dose modifications in BPd responders**

Belamaf dose modifications, n (%)	Responders (n=120)	
	Dose delays	Dose reduction
Any dose modification	119 (>99)	83 (69)
No. of dose modifications per patient		
0	1 (<1)	35 (29)
1	15 (13)	80 (67)
2	16 (13)	3 (3)
≥3	88 (74)	0
Not evaluable	–	2 (2)
Duration of dose delays[a]		
≤4 weeks	199 (34)	Not applicable
>4-8 weeks	135 (23)	
>8 weeks	261 (44)	

belamaf, belantamab mafodotin; BPd, belamaf, pomalidomide and dexamethasone.

Post hoc analysis.

[a] Percentage is out of the total non-missing delay durations. Delay duration is missing if dosing did not resume prior to data cutoff, where the delay was ongoing or patient subsequently discontinued treatment.

Conclusions

Dose modifications helped manage ocular events by individualising the dosing schedule per patient tolerability

Efficacy was maintained in the majority of patients who required extended belamaf dosing intervals

- Responses were maintained or deepened in the majority of patients following the first dose delay (≥2 cycles), including in those who had a dose delay after 1 or 2 doses of belamaf
  - Most patients (92%) with an inadequate response (≤ PR) prior to the first dose delay (>8 weeks) achieved ≥ PR, and the majority (73%) achieved deep response (≥ VGPR)
- Median PFS was not reached in patients who required extended belamaf dose delay (≥12 weeks)

Results

Table 5: **Best response in patients who had grade ≥2 ophthalmic exam finding**[a]

Patients with ≥1 grade ≥2 ophthalmic exam finding	BPd
Experienced ≥1 event (grade ≥2), n/N (%)	123/150 (82)
Continued belamaf following onset of first event, n/N (%)	120/123 (98)
No. of additional doses after event, median (range)	5 (1-21)
Best response, n/N (%)[b]	
≥ PR	106/120 (88)
≥ VGPR	90/120 (75)

belamaf, belantamab mafodotin; BPd, belamaf, pomalidomide and dexamethasone; KVA, Keratopathy and Visual Acuity; 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 6: **Summary of best response before and during/after the first belamaf dose delay of ≥2 cycles**[a,b]

Best response before the first dose delay of >8 weeks (n=83)		Best response during/after the first dose delay of >8 weeks	
Response	n (%)	Response	n (%)
≤ PR[c]	37 (45)	≥ VGPR	27 (73)
		≥ PR	34 (92)
≥ VGPR	46 (55)	CR/sCR	36 (78)
		≥ VGPR	45 (98)

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 antimyeloma therapy or last contact date is >31 days. [c] Includes 3 patients who had non-evaluable response.

Table 7: **PFS in patients with belamaf dose delay (≥12 weeks)**

Patients with ≥6 months of treatment	BPd (n=122)
No. of patients with ≥1 dose delay of ≥12 weeks	93
PFS, median (95% CI), months	NR (NR-NR)

belamaf, belantamab mafodotin; BPd, belamaf, pomalidomide and dexamethasone; CI, confidence interval; NR, not reached; PFS, progression-free survival.

Post hoc analysis.

Abbreviations

AR, adverse reaction; BCMA, B-cell maturation antigen; BCVA, best-corrected visual acuity; belamaf, belantamab mafodotin; BPd, belamaf, pomalidomide and dexamethasone; CD, cluster of differentiation; CI, confidence interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; eCRF, electronic case report form; ICR, interquartile range; ITT, intent to treat; ISS, International Staging System; IV, intravenous; KVA, Keratopathy and Visual Acuity; MMAF, monomethyl auristatin F; MOA, mechanism of action; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; PVd, pomalidomide, bortezomib and dexamethasone; Q4W, every 4 weeks; Q8W, every 8 weeks; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; sCR, stringent complete response; SOC, standard of care; 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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