The Impact of Patient-Reported Adverse Events on Quality of Life: An Analysis of the DREAMM-7 and DREAMM-8 Randomized Controlled Trials

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Background

- Belamaf is being investigated in 2 separate pivotal phase 3 trials in patients with RRMM who received ≥1 prior therapy
  - The DREAMM-7 trial (NCT04246047) demonstrated significant PFS benefit with BVd vs DVd (HR, 0.41; 95% CI, 0.31- 0.53; *P*<.001)[1]
  - The DREAMM-8 trial (NCT04484623) demonstrated significant PFS benefit with BPd vs PVd in lenalidomide-exposed patients (HR, 0.52; 95% CI, 0.37-0.73; *P*<.001)[2]
- In both studies, PRO analyses showed that patients' HRQOL was stable over time and comparable between arms[1,2]
- Patient-reported symptomatic AEs can impact patients' QOL and reduce the tolerability of a treatment, which may lead to treatment discontinuation and negatively impact clinical outcomes[3,4]
- Blurred vision is a commonly reported ocular AE with belamaf that has been managed by dose modifications in DREAMM-7 and DREAMM-8,[1,2] and the impact of blurred vision on patients is of particular interest
- The objective of this analysis was to use quantitative data from both trials to evaluate the impact of patient-reported symptomatic AEs, including blurred vision, on HRQOL

Methods

- Study designs for DREAMM-7 and DREAMM-8 are shown in **Figure 1**
  - Enrollment criteria and belamaf dosing regimens differed slightly between trials
  - PFS was the primary endpoint in both studies
  - PROs were collected at prespecified time points as secondary and exploratory endpoints in both studies
- The current post hoc analysis used data from several PRO assessments collected during the study, including the PRO-CTCAE; EORTC QLQ-C30 GHS/QOL, physical functioning, and role functioning domains; and EQ-5D VAS (**Table 1**)
- Linear regressions were performed using pooled data from both treatment arms of each study or using data from each arm individually (pooled time points) (**Figure 2**)
  - PRO-CTCAE composite grades (ranging from 0-3, with a higher grade indicating higher frequency/severity/interference) were calculated using established methods[3] and used as the independent variable in each linear regression analysis
  - EORTC QLQ-C30 GHS/QOL, physical functioning, and role functioning domains and EQ-5D VAS were used as the dependent variables

Results

- For both trials, characteristics of the patients and prior treatments were well balanced between arms[1,2]; pooled data for both arms of each trial are summarized in **Table 2**
- Adherence to PRO assessments was ≈90% for most visits while on treatment

DREAMM-7 and DREAMM-8 pooled data

- Among the AEs analyzed for both trials (**Tables 3 and 4**):
  - **Fatigue** had the greatest negative impact on HRQOL, with the largest negative estimated regression parameters for GHS/QOL, physical functioning, role functioning, and EQ-5D VAS and nominal *P* values of <.05 for all 4 measures
  - **Decreased appetite** also showed large negative estimated regression parameters and nominal *P* values of <.05 across all 4 measures
  - In contrast, **blurred vision** had a relatively minor impact, with smaller estimated regression parameters and nominal *P* values that were not consistently <.05
- Distribution of GHS/QOL and EQ-5D VAS scores according to PRO-CTCAE composite grades further illustrates these trends (**Figures 4-7**)
  - For fatigue and decreased appetite, a clear trend for worsening GHS/QOL and EQ-5D VAS scores was observed as PRO-CTCAE composite grades worsened; in contrast, GHS/QOL and EQ-5D VAS scores were more stable across PRO-CTCAE composite grades for blurred vision

Table 2: **Demographic and baseline characteristics**

	DREAMM-7 (N=494)	DREAMM-8 (N=302)
Male, n (%)	272 (55)	181 (60)
Age, median (range), years	64.5 (32-89)	67.0 (34-86)
Hispanic/Latino ethnicity, n (%)	71 (14)	17 (6)
Race, n (%)	(N=491)	(N=301)
Asian	61 (12)	37 (12)
Black or African American	20 (4)	0
White	409 (83)	260 (86)
Mixed race/Native Hawaiian/other Pacific Islander	1 (<1)	4 (1)
No. of prior lines of therapy, median (range)	1.0 (1-7)	1.0 (1-9)

Results

Table 3: **Linear regression results for DREAMM-7 (pooled arms)**

Estimated parameter[a]	GHS/QOL (n=10,783)	Physical functioning (n=10,787)	Role functioning (n=10,787)	EQ-5D VAS (n=5401)
Fatigue	−7.94*	−8.71*	−13.88*	−6.52*
Decreased appetite	−3.22*	−3.90*	−3.92*	−2.49*
Mouth/throat sores	−2.33*	−1.43*	−0.19	−2.40*
Pain in the abdomen	−1.46*	−0.81*	−1.35*	−1.42*
Nosebleeds	−1.14	−0.55	−1.76	−2.57*
Vomiting	−1.11	−1.20	−5.49*	1.37
Numb/tingly hands/feet	−0.98*	−2.60*	−2.79*	−1.50*
Shortness of breath	−0.82*	−3.29*	−3.94*	−0.20
Blurred vision	−0.56*	0.32	−1.42*	−0.02
Nausea	−0.49	−1.59*	−1.94*	−0.99
Pain/burning urination	−0.48	−3.12*	0.01	−0.89
Loose/watery stools	−0.04	0.68*	0.06	0.05
Constipation	0.01	−0.47	−1.46*	−0.61
Problems tasting food/drink	0.10	1.07*	1.18*	−0.46
Watery eyes	0.11	0.67*	−0.10	−0.07
Shivering/shaking chills	0.24	−2.19*	−0.80	−0.42
Cough	0.47	0.56	0.92*	−0.01
Itchy	0.56	0.41	0.94*	0.80*
R^2	0.25	0.37	0.41	0.24

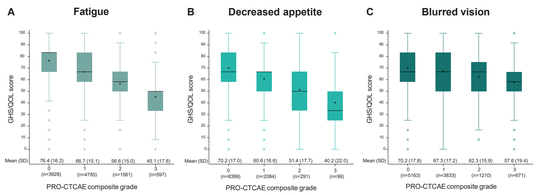
Post hoc analysis. Asterisk indicates P<.05 (nominal, not α controlled). AEs are listed from lowest to highest estimated parameter for GHS/QOL.
AE, adverse event; EQ-5D, EuroQol 5 dimension; GHS, global health status; QOL, quality of life; VAS, visual analog scale.
[a] Slope parameter estimates from the linear regression.

Table 4: **Linear regression results for DREAMM-8 (pooled arms)**

Estimated parameter[a]	GHS/QOL (n=4425)	Physical functioning (n=4416)	Role functioning (n=4417)	EQ-5D VAS (n=2409)
Fatigue	−7.40*	−10.84*	−10.68*	−6.41*
Decreased appetite	−4.44*	−5.52*	−7.07*	−3.33*
Nosebleeds	−2.63*	−1.02	3.02	−1.68
Shortness of breath	−2.23*	−1.84*	−2.22*	−1.37*
Mouth/throat sores	−1.88*	−1.72*	1.05	−1.66*
Numb/tingly hands/feet	−1.46*	−2.64*	−2.29*	−0.28
Cough	−1.36*	−1.38*	−0.51	−0.81
Vomiting	−1.11	−3.47*	−1.74	−1.80
Constipation	−0.91*	−0.89*	0.05	−1.25*
Problems tasting food/drink	−0.89	−0.68	0.62	−0.42
Pain in the abdomen	−0.71	−1.71*	−3.39*	−0.65
Itchy	−0.38	−1.68*	−0.71	−1.48*
Blurred vision	−0.35	1.34*	−0.66	−0.51
Shivering/shaking chills	−0.08	−0.52	−1.59*	−0.25
Loose/watery stools	0.06	−0.21	0.05	−0.07
Watery eyes	0.44	−0.45	−0.25	0.79
Pain/burning urination	0.68	0.45	1.45	2.28*
Nausea	0.82	0.46	−0.65	−0.10
R^2	0.35	0.49	0.35	0.29

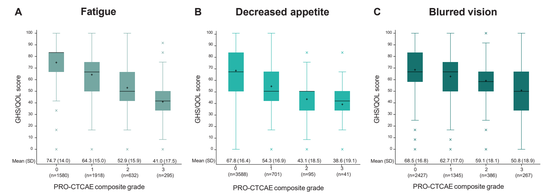
Post hoc analysis. Asterisk indicates P<.05 (nominal, not α controlled). AEs are listed from lowest to highest estimated parameter for GHS/QOL.
AE, adverse event; EQ-5D, EuroQol 5 dimension; GHS, global health status; QOL, quality of life; VAS, visual analog scale.
[a] Slope parameter estimates from the linear regression.

Figure 3. **Distribution of GHS/QOL scores according to PRO-CTCAE composite grades for (A) fatigue, (B) decreased appetite, and (C) blurred vision in DREAMM-7**



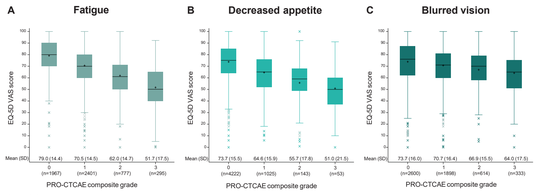
Post hoc analysis.
CTCAE, Common Terminology Criteria for Adverse Events; GHS, global health status; PRO, patient-reported outcome; QOL, quality of life.

Figure 4. **Distribution of GHS/QOL scores according to PRO-CTCAE composite grades for (A) fatigue, (B) decreased appetite, and (C) blurred vision in DREAMM-8**



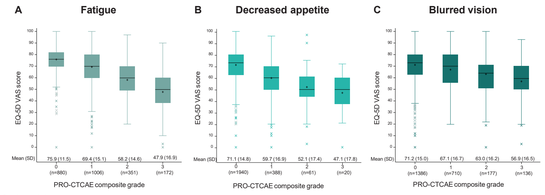
Post hoc analysis.
CTCAE, Common Terminology Criteria for Adverse Events; GHS, global health status; PRO, patient-reported outcome; QOL, quality of life.

Figure 5. **Distribution of EQ-5D VAS scores according to PRO-CTCAE composite grades for (A) fatigue, (B) decreased appetite, and (C) blurred vision in DREAMM-7**



Post hoc analysis.
CTCAE, Common Terminology Criteria for Adverse Events; EQ-5D, EuroQol 5 dimension; PRO, patient-reported outcome; VAS, visual analog scale.

Figure 6. **Distribution of EQ-5D VAS scores according to PRO-CTCAE composite grades for (A) fatigue, (B) decreased appetite, and (C) blurred vision in DREAMM-8**



Post hoc analysis.
CTCAE, Common Terminology Criteria for Adverse Events; EQ-5D, EuroQol 5 dimension; PRO, patient-reported outcome; VAS, visual analog scale.

Conclusions

- These data show that fatigue and decreased appetite were the patient-reported symptomatic AEs with the greatest impact on HRQOL in DREAMM-7 and DREAMM-8, regardless of treatment received
- Patient-reported blurred vision had a relatively minor impact on HRQOL, physical functioning, role functioning, and EQ-5D VAS
- These results are consistent with the results of prior analyses from both studies that investigated the impact of ocular AEs[1,2,8,9]
  - As previously reported in both studies, the ocular AEs that patients experienced were generally manageable with dose modifications, and an initial worsening of vision-related functioning early during treatment with belamaf combinations subsequently improved for most patients; overall, ocular AEs were characterized by a low rate of treatment discontinuation and relatively minor impact on patients' QOL[1,2,8,9]
  - Another previous analysis from DREAMM-7 showed that GHS/QOL scores in patients who experienced a clinically meaningful deterioration in vision-related function while on BVd were comparable to the overall GHS/QOL scores of all patients in the DVd arm[8]
- Overall, combined with PFS benefits and the relatively minor impact of ocular AEs on QOL,[1,2,8,9] these results further support belamaf combinations as a potential new standard of care in patients with RRMM

DREAMM-7 and DREAMM-8: results by treatment arm

- Analyses by arm in each trial were consistent with the pooled results overall, although some differences between arms were observed
- Notably, estimated parameters for the impact of blurred vision on role functioning were more negative for BVd/BPd than for DVd/PVd, while equivalent parameters for the impact of fatigue on physical functioning were more negative for DVd/PVd (**Table 5**)

Table 5: **Linear regression results for selected symptomatic AEs in DREAMM-7 and DREAMM-8 (by treatment arm)**

Estimated parameter[a]	GHS/QOL	Physical functioning	Role functioning	EQ-5D VAS
Fatigue				
DREAMM-7 BVd	−7.45*	−7.69*	−13.30*	−5.46*
DVd	−7.86*	−9.27*	−13.75*	−6.89*
DREAMM-8 BPd	−5.57*	−9.03*	−9.10*	−4.06*
PVd	−8.71*	−13.65*	−12.05*	−8.54*
Decreased appetite				
DREAMM-7 BVd	−3.17*	−4.54*	−3.94*	−2.21*
DVd	−2.69*	−3.18*	−4.69*	−1.57*
DREAMM-8 BPd	−4.03*	−4.81*	−5.91*	−2.11
PVd	−4.12*	−5.77*	−8.41*	−2.96*
Blurred vision				
DREAMM-7 BVd	−0.97*	−0.69*	−3.25*	−0.52
DVd	−1.12*	−0.62	−0.05	−0.41
DREAMM-8 BPd	−0.61	1.37*	−1.53*	−0.96
PVd	0.10	−0.26	0.53	−1.62

Post hoc analysis. Asterisk indicates P<.05 (nominal, not α controlled).
AE, adverse event; BPd, belamaf + pomalidomide + dexamethasone; BVd, belamaf + bortezomib + dexamethasone; DVd, daratumumab + bortezomib + dexamethasone; EQ-5D, EuroQol 5 dimension; GHS, global health status; PVd, pomalidomide + bortezomib + dexamethasone; QOL, quality of life; VAS, visual analog scale.
[a] Slope parameter estimates from the linear regression.

Limitations

- These were exploratory analyses that were not α controlled; *P* values are descriptive
- Low R^2 values indicate that the majority of the variation in PRO scores was not explained by the patient-reported AEs analyzed in this study; however, this was expected, as several other variables are expected to impact QOL, such as clinical response
- As analyses used pooled data across all time points, any impact of the timing of an AE or of time-dependent variables (such as onset/depth of clinical response) is not captured
- PRO-CTCAE composite grades were entered as continuous variables in the model, assuming linearity (a shift from grade 0 to 1 is similar to a shift from grade 2 to 3), which may be inaccurate
- Although arm-level analyses produced results consistent with the conclusions of the primary analyses, some differences between arms were observed

Abbreviations

AE, adverse event; belamaf, belantamab mafodotin; BPd, belamaf + pomalidomide + dexamethasone; BVd, belamaf + bortezomib + dexamethasone; DVd, daratumumab + bortezomib + dexamethasone; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, EuroQol 5 dimension; GHS, global health status; HR, hazard ratio; HRQOL, health-related quality of life; PFS, progression-free survival; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PVd, pomalidomide + bortezomib + dexamethasone; QOL, quality of life; RRMM, relapsed/refractory multiple myeloma; VAS, visual analog scale.

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