Belantamab Mafodotin With Pomalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma: A Comprehensive Exposure-Response Analysis of the DREAMM-8 Study

Targeted Oncology

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Supplementary Materials

1.0 Supplementary methods

1.1 Pomalidomide, bortezomib, and dexamethasone (PVd) dosing

For the PVd regimen used in DREAMM-8, pomalidomide was dosed at 4 mg orally on Days 1–14 every 3 weeks (Q3W); bortezomib at 1.3 mg/m^2 subcutaneously on Days 1, 4, 8, and 11 Q3W through Cycle 8, then Days 1 and 8 Q3W thereafter; and dexamethasone at 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11, and 12 Q3W through Cycle 8, then Days 1, 2, 8, and 9 Q3W thereafter.

1.2 Typical patient and deltas for odds and hazard ratio computation

The typical patient was defined as a male aged 65 years weighing 75 kg, with mild renal impairment (estimated glomerular filtration rate of 70 mL/min) and normal liver function (aspartate aminotransferase and alanine aminotransferase 20 IU/L and total bilirubin 0.4 mg/dL), as well as baseline values of soluble B-cell maturation antigen (sBCMA) 50 ng/mL, immunoglobulin G (IgG) 15 g/L, albumin 40 g/L, and body mass index 27 kg/m^2.

The following deltas were used for the computation of odds or hazard ratios (HRs):

- Cycle 1 belantamab mafodotin concentration at the end of 28 days delta of 0.5 ug/mL, representing the difference between the predicted Cycle 1 belantamab mafodotin concentration at the end of 28 days for a dose of 2.5 mg/kg and a dose of 1.9 mg/kg.

- Cycle 1 belantamab mafodotin average concentration (C_{avg}) delta of 2.0 ug/mL, representing the approximate difference between the predicted Cycle 1 belantamab mafodotin C_{avg} for a dose of 2.5 mg/kg and a dose of 1.9 mg/kg.

- Cycle 1 belantamab mafodotin maximum concentration (C_{max}) delta of 4.0 ug/mL, representing the approximate difference between the predicted belantamab mafodotin C_{max} for a dose of 2.5 mg/kg and a dose of 1.9 mg/kg.

- Cycle 1 cysteine maleimidocaproyl monomethyl auristatin F (cys-mcMMAF) C_{max} delta of 0.22 ng/mL, representing the difference between the predicted cys-mcMMAF C_{max} for a dose of 2.5 mg/kg and a dose of 1.9 mg/kg.

- Cycle 1 cys-mcMMAF C_{avg} delta of 0.05 ng/mL, representing the difference between the predicted cys-mcMMAF C_{avg} for a dose of 2.5 mg/kg and a dose of 1.9 mg/kg.

- Baseline IgG delta of 3 g/L, representing a 20% change from the typical value.

- Baseline albumin delta of 8 g/L, representing a 20% change from the typical value.

- Baseline sBCMA delta of 20 ng/mL, representing a 40% change from the typical value.

- Baseline β2-microglobulin delta of 100 nmol/L, representing the approximate difference between quartiles.

- Baseline lactate dehydrogenase delta of 50 U/L, representing the approximate change from either the first quartile or third quartile to the median.

- Baseline platelet count delta of 25×109/L, representing the difference between each grade of thrombocytopenia.

Supplementary Table S1. Summary of efficacy exposure-response results.

	Univariate analysis			**Final model**	
Endpoint	**Univariate Covariates**	**ΔOFV**	**Univariate p-value**	**Parameters**	**OR or HR (95% CI)**
Probability of overall response	Extramedullary disease	7.62	0.006	Null model	
Probability of ≥VGPR	Extramedullary disease	32.01	<0.001	Extramedullary disease	0.0378 (0.00581–0.14)
	Belantamab mafodotin C_{avg28}	14.17	<0.001		
	Belantamab mafodotin C_{tau28}[a]	14.04	<0.001		
	Baseline albumin	12.34	<0.001		
	Prior anti-CD38 treatment	12.00	0.001		
	ECOG PS 2	8.85	0.003		
	ECOG PS 0	9.68	0.008		
	Baseline sBCMA	6.64	0.01		
Probability of ≥CR	Belantamab mafodotin C_{avg28}	22.09	<0.001	Belantamab mafodotin C_{avg28}	3.4 (1.98–6.24)

	Extramedullary disease	15.75	<0.001	Prior anti-CD38 treatment	0.183 (0.0606–0.476)
	Prior anti-CD38 treatment	12.97	<0.001		
	Baseline albumin	10.10	0.001		
	Baseline IgG	9.30	0.002		
Probability of MRD negativity (sCR/CR)	Belantamab mafodotin C_{avg28}	12.08	0.001	Belantamab mafodotin C_{avg28}	2.53 (1.48–4.58)
	Prior anti-CD38 treatment	8.00	0.005		
	>1 prior LOT	7.88	0.005		
Progression-free survival	Baseline sBCMA	25.26	<0.001	Baseline sBCMA	1.08 (1.05–1.11)
	Baseline B2M	15.71	<0.001		
	Baseline LDH	10.65	0.001		
	Belantamab mafodotin C_{max}	9.21	0.002		
	Prior anti-CD38 treatment	8.76	0.003		
	Extramedullary disease	7.79	0.005		

	Refractory to both IMDs and PIs	7.24	0.007		
	Prior LOTs	9.84	0.007		
	Cytogenic risk[b]	6.69	0.01		
Duration of response	Baseline sBCMA	16.09	<0.001	Baseline sBCMA	1.09 (1.05–1.12)
	Baseline B2M	15.29	<0.001	Prior anti-CD38 treatment	3.56 (1.78–7.12)
	>1 prior LOT	9.43	0.002		
	Prior LOTs	11.62	0.003		
	Prior anti-CD38 treatment	8.59	0.003		
	Extramedullary disease	7.61	0.006		
	Baseline LDH	7.18	0.007		
Time to response	MM IgG type	15.70	<0.001	MM IgG type	0.406 (0.276–0.597)
	Extramedullary disease	14.09	<0.001	Extramedullary disease	0.271 (0.135–0.547)
	Baseline IgG	7.05	0.008		
	Baseline albumin	6.83	0.009		

	Belantamab mafodotin C_{avg28}	6.18	0.013		

[a]In the full model, belantamab mafodotin C_{tau28} had an odds ratio of 1.52 (95% CI 1.12–2.11) for probability of ≥VGPR. [b]Cytogenic risk was imputed as "no" for one patient for whom cytogenic risk status was missing.

For the univariate analyses, the top 3 covariates resulting in ΔOFV >6.63 relative to the null model were included. Additionally, any covariates resulting in a ΔOFV >10.83 were included. Only the strongest exposure covariate was included; if Cycle 1 belantamab mafodotin C_{avg} was not the strongest exposure covariate, it was included for reference and comparison across the efficacy and safety endpoints.

B2M, β2 microglobulin; C_{avg}, average concentration; C_{avg28}, average concentration over 28 days; CI, confidence interval; C_{max}, maximum concentration; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IgG, immunoglobulin G; IMD, immunomodulatory drug; LDH, lactate dehydrogenase; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; OFV, objective function value; OR, odds ratio; PI, proteasome inhibitor; sBCMA, soluble baseline B-cell maturation antigen; sCR, stringent complete response; ≥VGPR, very good partial response or better.

Supplementary Table S2. Incidence of safety events from DREAMM-8 that were included in the exposure-response analysis.[a]

	N=150
OEFs, n (%)	
Grade ≥2 OEF (KVA scale)	131 (87.3)
Grade ≥2 BCVA event (KVA scale)	124 (82.7)
Grade ≥2 corneal exam finding (KVA scale)	120 (80.0)
Grade ≥3 OEF (KVA scale)	116 (77.3)
Worsening of BCVA to 20/50 or worse in one eye[b]	95 (63.3)
Grade ≥3 corneal exam finding (KVA scale)	93 (62.0)
Grade ≥3 BCVA event (KVA scale)	90 (60.0)
Worsening in BCVA as defined by ΔlogMar ≥0.3 in the better-seeing eye	76 (50.7)
Worsening of BCVA to 20/50 or worse in both eyes[b]	60 (40.0)
Ocular adverse events, n (%)	
Grade ≥2 ocular adverse events (CTCAE grade)	105 (70.0)
Grade ≥3 ocular adverse events (CTCAE grade)	64 (42.7)
Dose modifications, n (%)	

Dose modification led by TEAE[b]	124 (82.7)
Dose delay/interruption	120 (80.0)
Dose reduction[b]	89 (59.3)
Dose discontinuation[c]	19 (12.7)
Grade ≥3 thrombocytopenia derived using clinical laboratory data, n (%)	60 (40.0)

[a]KVA events were sponsor-graded. [b]Regardless of baseline status. [c]Dose modifications of any treatment in the belantamab mafodotin, pomalidomide, and dexamethasone regimen are reported.

BCVA, best corrected visual acuity; CTCAE, Common Terminology Criteria for Adverse Events; KVA, keratopathy and visual acuity; logMAR, logarithm of the minimum angle of resolution; OEF, ophthalmic exam finding; TEAE, treatment-emergent adverse event.

77 **Supplementary Table S3.** Summary of oAE/OEF-related safety exposure-response results[a]

	Univariate analysis			Final model	
Endpoint	**Univariate covariates**	**ΔOFV**	**Univariate p-value**	**Parameter**	**OR or HR (95% CI)**
Probability of grade ≥2 ocular adverse event (CTCAE)	$C_{max,\ MMAF}$	10.44	0.001	Null model	
	Baseline sBCMA	8.32	0.004		
	European country	6.94	0.008		
Time to first grade ≥2 ocular adverse event (CTCAE)	Belantamab mafodotin C_{avg28}	15.06	<0.001	Belantamab mafodotin C_{avg28}	1.71 (1.3–2.25)
	European country	8.64	0.003		
Probability of grade ≥3 ocular adverse events (CTCAE)	Baseline BCVA best eye	9.94	0.002	Null model	
	Baseline age group	9.91	0.007		
	$C_{max,\ MMAF}$	6.78	0.009		
Time to first grade ≥3 ocular adverse event (CTCAE)	Baseline age group	14.77	0.001	Age group 65 to <75 years	0.538 (0.31–0.931)
	Baseline BCVA best eye	8.65	0.003	Age group ≥75 years	2.29 (1.17–4.51)

Probability of grade ≥2 OEF (KVA)	Belantamab mafodotin C_{tau28}	11.54	0.001	Belantamab mafodotin C_{avg28}	2.73 (1.42–5.57)
	Belantamab mafodotin C_{avg28}	9.34	0.002		
	Baseline sBCMA	8.92	0.003		
Time to first grade ≥2 OEF (KVA)	Belantamab mafodotin C_{tau28}	16.39	<0.001	Belantamab mafodotin C_{avg28}	1.57 (1.26–1.95)
	Belantamab mafodotin C_{avg28}	15.20	<0.001		
	Extramedullary disease	7.99	0.005		
	Cytogenic risk	7.14	0.008		
Probability of grade ≥3 OEF (KVA)	Baseline sBCMA	8.34	0.004	Null model	
Time to first grade ≥3 OEF (KVA)	Belantamab mafodotin C_{tau28}	9.68	0.002	Null model	
Probability of grade ≥2 BCVA worsening event (KVA)[b]	Baseline sBCMA	11.50	0.001	Baseline sBCMA	0.912 (0.859–0.962)
	European country	7.39	0.007		

	Baseline B2M	6.69	0.01		
Time to first grade ≥2 BCVA worsening event (KVA)[b]	European country	11.78	0.001	European country	0.509 (0.35–0.739)
	Treated in China	7.44	0.006		
Probability of grade ≥2 corneal exam finding (KVA)	Belantamab mafodotin C_{tau28}	14.45	<0.001	Belantamab mafodotin C_{avg28}	2.83 (1.61–5.28)
	Belantamab mafodotin C_{avg28}	13.74	<0.001		
	Baseline sBCMA	10.46	0.001		
Time to first grade ≥2 corneal exam finding (KVA)	Belantamab mafodotin C_{tau28}	13.98	<0.001	Belantamab mafodotin C_{avg28}	1.55 (1.23–1.95)
	Belantamab mafodotin C_{avg28}	13.34	<0.001		
	Extramedullary disease	7.56	0.006		
	Keratopathy at baseline	7.35	0.007		
Probability of grade ≥3 BCVA worsening event (KVA)[b]	Extramedullary disease	15.48	<0.001	Extramedullary disease	0.128 (0.035–0.373)

Time to first grade ≥3 BCVA worsening event (KVA)[b]	Extramedullary disease	9.78	0.002	Null model	
	Baseline BCVA best eye	6.90	0.009		
Time to first grade ≥3 corneal exam finding (KVA)	Belantamab mafodotin C_{tau28}	8.17	0.004	Null model	
Probability of worsening in BCVA defined by ΔlogMar ≥0.3 in the better-seeing eye[b]	Extramedullary disease	9.19	0.002	Null model	
Probability of worsening of BCVA to 20/50 or worse in one eye[b]	$C_{max, MMAF}$	11.89	0.001	$C_{max, MMAF}$	0.752 (0.612–0.894)
	Baseline sBCMA	11.15	0.001		
	Baseline BCVA worst eye	9.94	0.002		
	European country	8.74	0.003		
Probability of worsening of BCVA to 20/50 or worse in both eyes[b]	Baseline BCVA best eye	6.70	0.01	Null model	

[a]Probability of grade ≥3 corneal exam finding is not shown, as no significant covariates were identified in the univariate screening.

[b]Regardless of baseline status.

For the univariate analyses, the top 3 covariates resulting in ΔOFV >6.63 relative to the null model were included. Additionally, any covariates resulting in a ΔOFV >10.83 were included. Only the strongest exposure covariate was included; if Cycle 1 belantamab mafodotin C_{avg} was not the strongest exposure covariate, it was included for reference and comparison across the efficacy and safety endpoints.

B2M, β2 microglobulin; BCVA, best corrected visual acuity; C_{avg28}, average concentration over 28 days; CI, confidence interval; C_{max}, maximum concentration; $C_{max, MMAF}$, maximum concentration of cys-mcMMAF; C_{tau28}, concentration at the end of 28 days; CTCAE, Common Terminology Criteria for Adverse Events; HR, hazard ratio; KVA, keratopathy and visual acuity; logMAR, logarithm of the minimum angle of resolution; OEF, ophthalmic exam finding; OFV, objective function value; OR, odds ratio; sBCMA, soluble baseline B-cell maturation antigen.

Supplementary Table S4. Summary of other AEs and dose modification safety exposure-response results.

	Univariate analysis			Final model	
Endpoint	**Univariate covariates**	**ΔOFV**	**Univariate p-value**	**Parameter**	**OR or HR (95% CI)**
Probability of grade ≥3 thrombocytopenia	Baseline platelet count	28.39	<0.001	Baseline platelet count	0.672 (0.558–0.791)
	White race	11.70	0.001		
	Northeast Asian country	10.58	0.001		
	Asian race	8.74	0.003		
	Northeast Asian race	8.74	0.003		
Probability of dose discontinuation	ISS stage I or stage II/III at screening	12.94	<0.001	ISS stage II/III	0.0721 (0.00395–0.365)
	ISS stage I or stage II or stage III at screening	13.85	0.001		
	Belantamab mafodotin C_{avg28}	7.25	0.007		
Probability of dose reduction	Baseline B2M	13.15	<0.001	Baseline B2M	0.653 (0.48–0.839)

	ISS stage I or stage II or stage III at screening	11.62	0.003		
	$C_{avg28, MMAF}$	10.66	0.001		
	ISS stage I or stage II/III at screening	10.32	0.001		
	Baseline sBCMA	8.22	0.004		
	Extramedullary disease	8.13	0.004		
	Prior anti-CD38 treatment	8.10	0.004		
Probability of dose delay/interruption	Belantamab mafodotin C_{max}	11.26	0.001	Belantamab mafodotin C_{avg28}	1.95 (1.15–3.43)
	European country	7.20	0.007		
	Baseline sBCMA	6.75	0.009		
	Belantamab mafodotin C_{avg28}	6.13	0.013		
Probability of TEAE-led	$C_{max, MMAF}$	14.07	<0.001	$C_{max, MMAF}$	0.723 (0.582–0.866)

dose modification	ISS stage I or stage II or stage III at screening	9.49	0.009		
	ISS stage I or stage II/III at screening	9.24	0.002		
	Baseline sBCMA	8.48	0.004		
	Extramedullary disease	6.86	0.009		
	Baseline B2M	6.74	0.009		

For the univariate analyses, the top 3 covariates resulting in ΔOFV >6.63 relative to the null model were included. Additionally, any covariates resulting in a ΔOFV >10.83 were included. Only the strongest exposure covariate was included; if Cycle 1 belantamab mafodotin C_{avg} was not the strongest exposure covariate, it was included for reference and comparison across the efficacy and safety endpoints.

AE, adverse event; B2M, β2 microglobulin; C_{avg}, average concentration; C_{avg28}, average concentration over 28 days; $C_{avg28,MMAF}$, MMAF average concentration over 28 days; C_{max}, maximum concentration; $C_{max,\ MMAF}$, Cycle 1 cys-mcMMAF maximum concentration; HR, hazard ratio; ISS, International Staging System; MMAF, monomethyl auristatin F; OFV, objective function value; OR, odds ratio; sBCMA, soluble B-cell maturation antigen; TEAE, treatment-emergent adverse event.