Pivotal DREAMM-2 Study: Single-Agent Belantamab Mafodotin (Belamaf; GSK2857916) in Patients With Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to Proteasome Inhibitors, Immunomodulatory Agents, and Refractory and/or Intolerant to Anti-CD38 Monoclonal Antibodies (mAbs), Including Subgroups With Renal Impairment (RI) and High-Risk (HR) Cytogenetics

Poster No. MM-219

Sagar Lonial[1], Hans Chulhee Lee[2], Ashraf Badros[3], Suzanne Trudel[4], Ajay K Nooka[1], Ajai Chari[5], Al-Ola Abdallah[6], Natalie Scott Callander[7], Douglas Weston Sborov[8], Attaya Suvannasankha[9], Katja Weisel[10], Peter M Voorhees[11], Malin Hultcrantz[12], Edward N Libby[13], Paul G Richardson[14], Paula Rodriguez Otero[15], Britta Besemer[16], Thierry Facon[17], Axel Hoos[18], Eric Zhi[18], January Baron[18], Trisha Piontek[18], Roxanne C Jewell[19], Eric Lewis[19], Joanna Opalinska[18], Ira Gupta[18], Adam D Cohen[20]

[1]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]University of Maryland at Baltimore, Baltimore, MD, USA; [4]Princess Margaret Cancer Centre, Toronto, ON, Canada; [5]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [6]University of Kansas Cancer Center, Fairway, KS, USA; [7]University of Wisconsin, Carbone Cancer Center, Madison, WI, USA; [8]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [9]Indiana University Cancer Center, Indianapolis, IN, USA; [10]Medical Center of Hamburg-Eppendorf, Hamburg, Germany; [11]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [12]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [13]Division of Medical Oncology, University of Washington, Seattle, WA, USA; [14]Dana-Farber Cancer Institute, Boston, MA, USA; [15]Clinica Universidad de Navarra-Pamplona, Navarra, Spain; [16]Universitaetsklinikum Tuebingen, Tuebingen, Germany; [17]CHRU de Lille, Hôpital Claude Huriez, Lille, France; [18]GlaxoSmithKline, Philadelphia, PA, USA; [19]GlaxoSmithKline, Research Triangle Park, NC, USA; [20]University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA, USA

Aims

To present efficacy and safety outcomes analyzed post hoc at 13-months' follow-up in the overall DREAMM-2 (NCT03525678) study population and in subgroups of patients with HR cytogenetics or RI, in response to treatment with single-agent belamaf.

Background

Patients with RRMM refractory to an anti-CD38 therapy have a particularly poor prognosis with currently available treatments, with an expected median progression-free survival (PFS) of 3.4 months and median overall survival (OS) of 9.3 months.[1–4] Subgroups of patients with RRMM and RI or HR-cytogenetics have a particularly high unmet need and require novel, efficacious, and well-tolerated treatment options.[5,6]

- RI is a frequent complication and poor prognostic factor in RRMM, which may limit treatment with standard regimens.[5]
- Patients with RRMM and HR cytogenetic abnormalities have a poor prognosis with outcomes varying by treatment choice.[1]

Belamaf is a first-in-class, antibody-drug conjugate that binds to B-cell maturation antigen (BCMA) expressed on all malignant plasma cells.[6] Belamaf eliminates multiple myeloma cells by a multimodal mechanism of action, including apoptosis, release of markers characteristic of immunogenic cell death, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis.[6,7]

In the primary analysis of DREAMM-2, single-agent belamaf demonstrated deep and durable responses in patients with heavily pretreated RRMM. Overall response rates (ORRs) were 31% and 34%, and median PFS was 2.9 months and 4.9 months, in the 2.5-mg/kg and 3.4-mg/kg groups (median follow-up of 6.3 and 6.9 months), respectively.[8] Median duration of response (DoR) was not reached; OS data were not mature. The safety profile was manageable with dose modifications.

Methods

DREAMM-2 is an ongoing, open-label, two-arm, randomized, multicenter study of single-agent belamaf (2.5 or 3.4 mg/kg, intravenously [IV] every 3 weeks [Q3W] until disease progression or unacceptable toxicity) in patients with RRMM (**Figure 1**).[8]

Renal function was assessed according to estimated glomerular filtration rate (eGFR) and categorized as below. Patients with eGFR <30 mL/min/1.73 m^2 were ineligible.[8]

- Normal (≥90 mL/min/1.73 m^2); mildly impaired (≥60–<90 mL/min/1.73 m^2); moderately impaired (≥30–<60 mL/min/1.73 m^2).

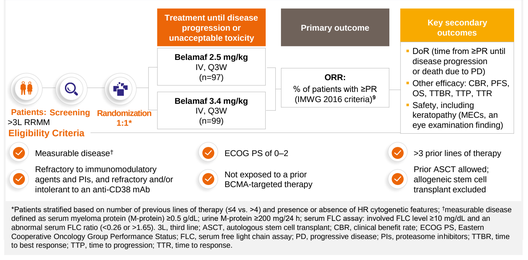
HR and standard risk (SR) patient groups were determined by cytogenetic profile (testing was performed locally)[8,9]:

- HR: patients with any of t(4;14), t(14;16), 17p13del, or 1q21+; SR: patients without any of the above cytogenetic features.

The primary efficacy endpoint was ORR (≥partial response [PR]) according to International Myeloma Working Group (IMWG) 2016 criteria,[9] as assessed by an independent review committee.

Safety endpoints included adverse events (AEs), serious AEs (SAEs), AEs leading to dose delays and interruptions, study treatment–related AEs, and AEs of special interest (AESI), which included keratopathy (microcyst-like epithelial changes [MECs] to the cornea; an eye examination finding with or without symptoms).

Figure 1. Study design[10]



*Patients stratified based on number of previous lines of therapy (≤4 vs. >4) and presence or absence of HR cytogenetic features; †measurable disease defined as serum myeloma protein (M-protein) ≥0.5 g/dL; urine M-protein ≥200 mg/24 h; serum FLC assay: involved FLC level ≥10 mg/dL and an abnormal serum FLC ratio (<0.26 or >1.65). 3L, third line; ASCT, autologous stem cell transplant; CBR, clinical benefit rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FLC, serum free light chain assay; PD, progressive disease; PIs, proteasome inhibitors; TTBR, time to best response; TTP, time to progression; TTR, time to response.

Results

Patient demographics

Patient demographics and baseline disease characteristics for the overall population and for the subgroups of patients with RI and HR cytogenetics have been previously reported.[10–12]

- At screening, approximately half of the patients in DREAMM-2 had mild RI (2.5 mg/kg: 49% [48/97]; 3.4 mg/kg: 53% [52/99]); approximately one-quarter had moderate RI (2.5 mg/kg: 25% [24/97]; 3.4 mg/kg: 22% [22/99]).[11]
- The most common cytogenetic risk factors in patients with HR cytogenetics were 1q21+ (2.5 mg/kg: 61% [25/41]; 3.4 mg/kg: 63% [30/48]) and 17p13del (2.5 mg/kg: 39% [16/41]; 3.4 mg/kg: 46% [22/48]).[12]

Overall population efficacy and safety

Efficacy and safety outcomes for the overall population of patients in each dose group after 13 months of follow-up (as of January 2020) are summarized in **Tables 1** and **2**, respectively.[10]

Details of dose modifications in DREAMM-2 are presented in poster MM-250 at this meeting.

Table 1. Clinical responses in the overall population[10]

Independent review committee–assessed response*	Belamaf 2.5 mg/kg (N=97)	Belamaf 3.4 mg/kg (N=99)
ORR, n (%) (97.5% CI)	31 (32) (21.7–43.6)	35 (35) (24.8–47.0)
DoR estimates, median, months (95% CI estimates)	11.0 (4.2–NR)	6.2 (4.8–NR)
PFS, median, months (95% CI)	2.8 (1.6–3.6)	3.9 (2.0–5.8)
OS estimates, median, months (95% CI estimates)	13.7 (9.9–NR)	13.8 (10.0–NR)

*Best response as assessed by independent review committee using IMWG 2016 criteria.[9] Intention-to-treat population (all randomly assigned patients, regardless of treatment administration). All patients who received ≥2 doses of belamaf and completed ≥1 disease assessment after the second dose were evaluable for response. ORR: sCR+CR+VGPR+PR. CI, confidence interval; CR, complete response; NR, not reached; sCR, stringent complete response; VGPR, very good partial response.

Table 2. ≥Grade 3 AEs occurring in ≥10% of patients in either group in the overall population[10]

Patients with AE, n (%)*	Belamaf 2.5 mg/kg (N=95)	Belamaf 3.4 mg/kg (N=99)
Any event	80 (84)	83 (84)
Keratopathy (MECs)†	44 (46)	42 (42)
Thrombocytopenia‡	21 (22)	32 (32)
Anemia	20 (21)	27 (27)
Lymphocyte count decreased	12 (13)	7 (7)
Neutropenia§	10 (11)	16 (16)
Pneumonia	7 (7)	13 (13)

Events shown in decreasing order of incidence in the 2.5-mg/kg group. *Events reported based on CTCAE v4.03 (with the exception of keratopathy [MECs, an eye examination finding]) in the safety population (all patients who received ≥1 dose of study treatment); †represents severe MECs based on corneal examination findings and changes in BCVA from baseline (does not include patient-reported symptoms); ‡includes preferred terms thrombocytopenia, decreased platelet count, and cerebral hemorrhage (2 cases within the 3.4-mg/kg group only); §includes preferred terms neutropenia, febrile neutropenia, and neutrophil count decreased. BCVA, best-corrected visual acuity; CTCAE v4.03, Common Terminology Criteria for Adverse Events version 4.03.

Efficacy in patients with RI

Belamaf treatment led to clinical responses in patients with mild and moderate RI.

ORR was comparable in patients with normal renal function and mild and moderate RI (**Table 3**).

Table 3. Clinical responses in patients with normal renal function and mild and moderate RI

Independent review committee–assessed response*	Belamaf 2.5 mg/kg			Belamaf 3.4 mg/kg		
	Normal renal function (n=19)	Mild RI (n=48)	Moderate RI (n=24)	Normal renal function (n=17)	Mild RI (n=52)	Moderate RI (n=22)
ORR, n (%) (95% CI)	7 (37) (16.3–61.6)	16 (33) (20.4–48.4)	8 (33) (15.6–55.3)	6 (35) (14.2–61.7)	21 (40) (27.0–54.9)	6 (27) (10.7–50.2)
DoR estimates, median, months (95% CI estimates)	4.2 (1.4–NR)	12.5 (2.2–NR)	13.1 (4.2–NR)	6.2 (2.1–NR)	NR (4.2–NR)	5.6 (2.3–NR)
PFS, median, months (95% CI)	3.0 (1.3–6.2)	2.2 (2.0–3.6)	3.7 (1.0–12.5)	2.8 (1.3–7.3)	3.9 (1.4–7.0)	3.4 (0.8–6.4)
OS estimates, median, months (95% CI estimates)	14.9 (7.7–NR)	13.7 (11.4–NR)	NR (5.1–NR)	10.0 (4.0–NR)	13.8 (9.4–NR)	13.8 (4.4–NR)

*Best response as assessed by independent review committee using IMWG 2016 criteria.[9] Intention-to-treat population (all randomly assigned patients, regardless of treatment administration). All patients who received ≥2 doses of belamaf and completed ≥1 disease assessment after the second dose were evaluable for response. ORR: sCR+CR+VGPR+PR.

Safety in patients with renal impairment

Overall Grade 3–4 AEs were comparable across all groups (**Table 4**).

Across both cohorts, keratopathy (MECs, an eye examination finding), thrombocytopenia, and anemia were the most frequently reported Grade 3–4 AEs, irrespective of baseline renal function.

Few patients, with available post-baseline renal laboratory values, developed signs of active renal conditions (albumin creatinine ratio ≥500 mg/g):

- Mild RI subgroup: 1/45 patients in 2.5-mg/kg cohort, 2/37 patients in 3.4-mg/kg cohort
- Moderate RI subgroup: 2/20 patients in 2.5-mg/kg cohort, 5/20 patients in 3.4-mg/kg cohort

Table 4. Most frequent Grade 3–4 AEs (≥10% in any group) and renal laboratory changes

Grade 3–4 AE, n (%)	Belamaf 2.5 mg/kg			Belamaf 3.4 mg/kg		
	Normal renal function (n=19)	Mild RI (n=48)	Moderate RI (n=24)	Normal renal function (n=18)	Mild RI (n=52)	Moderate RI (n=22)
Hematologic AEs						
Anemia	1 (5)	9 (19)	7 (29)	5 (28)	13 (25)	9 (41)
Lymphocyte count decreased	2 (11)	8 (17)	2 (8)	NR	5 (10)	2 (9)
Neutropenia*	2 (11)	4 (8)	3 (13)	4 (22)	8 (15)	4 (18)
Thrombocytopenia†	3 (16)	9 (19)	8 (33)	5 (28)	16 (31)	11 (50)
Nonhematologic AEs						
AST increased	2 (11)	0 (0)	0 (0)	0 (0)	7 (13)	1 (5)
Fatigue	0 (0)	1 (2)	1 (4)	2 (11)	2 (4)	0 (0)
Hypercalcemia	0 (0)	3 (6)	3 (13)	NR	2 (4)	1 (5)
Hypertension	0 (0)	0 (0)	4 (17)	1 (6)	4 (8)	2 (9)
Hypoxia	NR	NR	NR	2 (11)	NR	1 (5)
Infusion-related reaction	0 (0)	0 (0)	3 (13)	0 (0)	0 (0)	1 (5)
γ-glutamyltransferase increased	1 (5)	2 (4)	1 (4)‡	1 (6)	4 (8)	3 (14)
Pneumonia	1 (5)	2 (4)	3 (13)	2 (11)	6 (12)	3 (14)
Ocular AEs						
Keratopathy (MECs)§	8 (42)	12 (25)	8 (33)	5 (28)	13 (25)	4 (18)
Renal laboratory changes¶						
Renal impairment defined by increased albumin creatinine ratio‖; n/N (%)	2/14 (14)	1/45 (2)	2/20 (10)	3/14 (21)	2/37 (5)	5/20 (25)

*Includes preferred terms neutropenia, febrile neutropenia, and neutrophil count decreased; †includes preferred terms thrombocytopenia and platelet count decreased. Three patients had a Grade 5 cerebral hemorrhage (2/52 [4%] in the 3.4-mg/kg mild RI subgroup; 1/22 [5%] in the 3.4-mg/kg moderate RI subgroup); ‡represents γ-glutamyltransferase abnormal; §eye examination finding; ¶data for patients with laboratory measures (ie, patients with missing laboratory measures were excluded); ‖patients with albumin creatinine ratio <500 mg/g at baseline and albumin creatinine ratio ≥500 mg/g at worst post baseline. AST, aspartate aminotransferase.

Efficacy in patients with HR cytogenetics

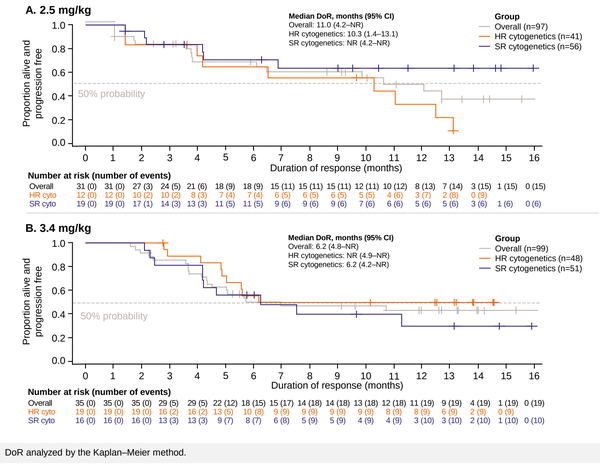
Efficacy outcomes were similar for patients with HR or SR cytogenetics (**Table 5**) and consistent with these outcomes observed in the overall population (**Table 1** and **Figure 2**).

Table 5. Clinical responses in patients with HR and SR cytogenetics

Independent review committee–assessed response*	Belamaf 2.5 mg/kg		Belamaf 3.4 mg/kg	
	HR cytogenetics (n=41)	SR cytogenetics (n=56)	HR cytogenetics (n=48)	SR cytogenetics (n=51)
ORR, n (%) (95% CI)	12 (29) (16.1–45.5)	19 (34) (21.8–47.8)	19 (40) (25.8–54.7)	16 (31) (19.1–45.9)
DoR estimates, median, months (95% CI estimates)	10.3 (1.4–13.1)	NR (4.2–NR)	NR (4.9–NR)	6.2 (4.2–NR)
PFS, median, months (95% CI)	2.1 (0.8–3.7)	2.9 (1.6–4.8)	5.8 (1.5–7.6)	3.1 (1.4–5.6)
OS estimates, median, months (95% CI estimates)	9.9 (4.3–NR)	17.0 (12.4–NR)	15.4 (12.5–NR)	10.1 (7.4–NR)

*Best response as assessed by independent review committee using IMWG 2016 criteria.[9] Intention-to-treat population (all randomly assigned patients, regardless of treatment administration). All patients who received ≥2 doses of belamaf and completed ≥1 disease assessment after the second dose were evaluable for response. ORR: sCR+CR+VGPR+PR.

Figure 2. Duration of response in patients with HR or SR cytogenetics and in the overall population



DoR analyzed by the Kaplan–Meier method.

Safety in patients with HR cytogenetics

Keratopathy (MECs, an eye examination finding) was the most common AE and AESI for patients with HR or SR cytogenetics (**Table 6**).

Generally, rates of anemia and thrombocytopenia were higher in HR versus SR patients.

Table 6. AESIs in Patients with HR and SR cytogenetics

N (%)	Belamaf 2.5 mg/kg		Belamaf 3.4 mg/kg	
	HR cytogenetics (n=41)	SR cytogenetics (n=54)	HR cytogenetics (n=48)	SR cytogenetics (n=51)
Keratopathy (MECs)*	24 (59)	43 (80)	38 (79)	36 (71)
Thrombocytopenia†	17 (41)	19 (35)	31 (65)	25 (49)
Anemia	11 (27)	15 (28)	20 (42)	18 (35)

*An eye examination finding; †includes thrombocytopenia, platelet count decreased, and cerebral hemorrhage (2 events in the 3.4-mg/kg arm only).

Conclusions

Single-agent belamaf represents an important new treatment option for patients with heavily pretreated RRMM, including those with high risk (HR) cytogenetics and renal impairment (RI).

In the overall population, deep and durable responses with single-agent belamaf were sustained with over a year of follow-up in this RRMM population.

- No new safety signals were identified with longer-term follow-up with single-agent belamaf, confirming its manageable safety profile.

The majority of patients included in this study had mild or moderate RI, representing a common, real-world complication in patients with RRMM and a poor prognostic factor.

- Efficacy and safety of single-agent belamaf were similar in patients with RI versus patients with normal renal function.

Efficacy and safety of single-agent belamaf were similar in patients with HR cytogenetics and in those with SR cytogenetics.

- Patients with HR cytogenetics maintain deep and durable clinical responses with single-agent belamaf, comparable to those reported in the overall population.
- The safety profile remained consistent with previous reports.

Disclosures

SL has received grant funding and personal fees from Celgene and Takeda, and personal fees from Amgen, Bristol-Myers Squibb, GlaxoSmithKline (GSK), Janssen, Merck, and Novartis. **HCL** has received grant funding and personal fees from Amgen, Celgene, Janssen, and Takeda; personal fees from GSK and Sanofi; and grant funding from Daiichi Sankyo. **AB** received consulting fees from Amgen. **ST** received consulting fees from Amgen, Celgene, and GSK; honoraria from Amgen Canada, Celgene, Janssen, Karyopharm, Sanofi, and Takeda; and research funding from Amgen, Celgene, Genentech, GSK, and Janssen. **AKN** received consulting fees from Amgen, Bristol-Myers Squibb, Celgene, GSK, Janssen Oncology, Karyopharm Therapeutics, Oncopeptides, Spectrum Pharmaceuticals, and Takeda; personal fees from GSK; and research funding from Amgen, Janssen Oncology, and Takeda. **AC** received consulting fees from Amgen, Antengene, Bristol-Myers Squibb, Celgene, GSK, Genzyme, Janssen Oncology, Karyopharm Therapeutics, Novartis, Oncopeptides, Seattle Genetics, Secura Bio, and Takeda; and research funding from Amgen, Celgene, Janssen, Novartis, Pharmacyclics, Seattle Genetics, and Takeda. **A-OA** declares no competing interests. **NSC** received research funding from Cellectar. **DWS** received consulting fees, honoraria, and personal fees from Janssen. **AS** received consulting fees from GSK, Janssen, and Karyopharm Therapeutics; research funding from Bristol-Myers Squibb, Celgene, GSK, and Janssen; and personal fees from GSK and Janssen. **KW** received consulting fees/honoraria from Adaptive, Amgen, Bristol-Myers Squibb, Celgene, GSK, Janssen, Karyopharm, Sanofi, and Takeda; and research funding from Amgen, Celgene, Janssen, and Sanofi. **PMV** has received personal fees from Adaptive Biotechnologies, Bristol-Myers Squibb /Celgene, Janssen, Novartis, Oncopeptides, and TeneoBio. **MH** received consulting fees from Intellisphere,LLC; and research funding from Amgen, DaichiSankyo, and GSK. **ENL** received consulting fees from Adaptive Biotechnologies, Akcea and Pharmacyclics. **PGR** received consulting fees from Celgene, Janssen, Jazz Pharmaceuticals, Karyopharm Therapeutics, Oncopeptides, Sanofi, and Takeda; and research funding from Bristol-Myers Squibb, Celgene, Oncopeptides, and Takeda. **PRO** received consulting fees from AbbVie, Celgene, GSK, Janssen, Kite, and Sanofi; and personal fees from Celgene. **BB** received travel and accommodation expenses and honoraria from Janssen-Cilag. **TF** has nothing to disclose. **AH, EZ, JB, TP, EL,** and **JO** are employees of and hold stocks and shares in GSK. **RCJ** and **IG** are employees of and hold stocks/shares in GSK and hold stocks/shares in Novartis. **ADC** has received grant funding from Bristol-Myers Squibb, GSK, and Novartis; personal fees from Janssen, Kite Pharma, Oncopeptides, Seattle Genetics, and Takeda; and personal fees and other association with Celgene and GSK.

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Further analyses of DREAMM-2 are presented at this meeting (posters MM-209 and MM-250).

For questions, please contact: sloni01@emory.edu

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