Pivotal DREAMM-2 Study: Single-agent Belantamab Mafodotin (GSK2857916) in Patients With Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to Proteasome Inhibitors (PIs), Immunomodulatory Agents, and Refractory and/or Intolerant to Anti-CD38 Monoclonal Antibodies (mAbs)

Poster No. 436

Sagar Lonial[1], Hans C Lee[2], Ashraf Badros[3], Suzanne Trudel[4], Ajay K Nooka[1], Ajai Chari[5], Al-Ola Abdallah[6], Natalie Callander[7], Douglas Sborov[8], Attaya Suvannasankha[9], Katja Weisel[10], Peter M. Voorhees[11], Axel Hoos[12], Eric Zhi[12], January Baron[12], Trisha Piontek[12], Roxanne C Jewell[13], Joanna Opalinska[12], Ira Gupta[12], Adam D Cohen[14]

[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, 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]GlaxoSmithKline, Philadelphia, PA, USA; [13]GlaxoSmithKline, Research Triangle Park, NC, USA; [14]Abramson Cancer Center, Philadelphia, PA, USA

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]

B cell maturation antigen (BCMA) is a cell-membrane receptor that is expressed on all malignant plasma cells and is essential for their proliferation and survival.[5]

Belantamab mafodotin (belamaf; GSK2857916) is a first-in-class antibody-drug conjugate that binds to BCMA and eliminates multiple myeloma cells by a multimodal mechanism of action, including apoptosis, release of immunogenic cell-death markers, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis.[5,6]

In the primary analysis of the DREAMM-2 study (NCT03525678), single-agent belamaf demonstrated deep and durable responses in heavily pretreated patients with 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.[7] Median duration of response (DoR) was not reached; OS data were not mature. The safety profile was acceptable with dose modifications.

Aim

To report the updated efficacy (including DoR and OS) and safety (including resolution of keratopathy; microcyst-like epithelial changes [MECs]) outcomes in the DREAMM-2 13 month follow-up.

Methods

DREAMM-2 is an ongoing, open-label, two-arm, randomized, multicenter, Phase II study of single-agent belamaf (2.5 or 3.4 mg/kg, IV every 3 weeks until disease progression or unacceptable toxicity) in patients with RRMM (**Figure 1**). Patients were enrolled between June 2018–January 2019.[6] Patients provided informed consent.

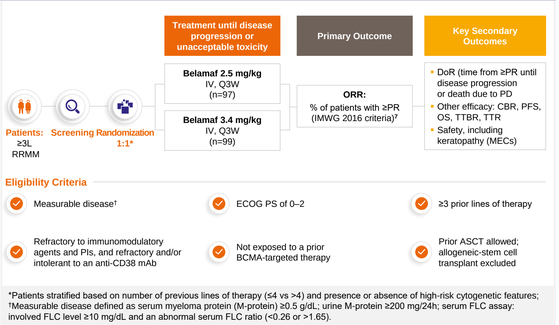
In the enrolled population, patients with International Staging System stage III disease (72/196), extramedullary disease (40/196), and high-risk cytogenetic features (17p13del, t[4;14], t[14;16], or 1q21+; 88/196) were well represented in both cohorts. Patients had a median (range) 7 (3–21) and 6 (3–21) prior lines of treatment in the 2.5-mg/kg and 3.4-mg/kg cohorts, respectively.[6]

The primary efficacy endpoint was ORR (≥ partial response [PR]) according to IMWG 2016 criteria,[8] as assessed by an independent review committee; key secondary efficacy outcomes were DoR, clinical benefit rate (CBR) (≥minimal response [MR]), time to response (TTR), PFS, and OS.

Safety endpoints included adverse events (AEs), serious AEs (SAEs), AEs leading to dose delays and interruptions, study TRAEs, and AESIs, which included keratopathy (MECs; may or may not be symptomatic).

The intention-to-treat population comprised all randomly assigned patients, regardless of treatment administration. For response-rate analyses, patients with unknown or missing data were treated as non-responders. Time-to-event analyses (DoR, TTR, time to progression [TTP], PFS and OS) were analysed by the Kaplan–Meier method.

Figure 1: Study design[6]



*Patients stratified based on number of previous lines of therapy (≤4 vs >4) and presence or absence of high-risk cytogenetic features; †Measurable disease defined as serum myeloma protein (M-protein) ≥0.5 g/dL; urine M-protein ≥200 mg/24h; serum FLC assay: involved FLC level ≥10 mg/dL and an abnormal serum FLC ratio (<0.26 or >1.65).

Results

Efficacy

At 13-month follow-up (as of January 2020; **Table 1**), deep responses were seen; more than half of responders (58% [18/31] and 66% [23/35] in the 2.5 and 3.4-mg/kg groups, respectively) achieved a VGPR or better.

- CBR was achieved in 35 patients (36%) and 40 patients (40%), respectively.

Table 1. Clinical response

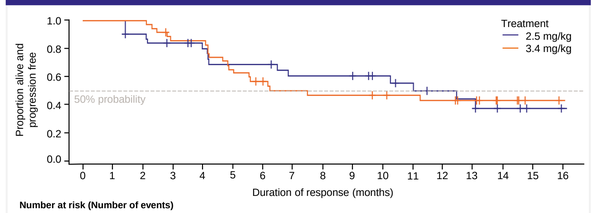
Independent Review Committee-Assessed Response*	Belamaf 2.5 mg/kg (N=97)	Belamaf 3.4 mg/kg (N=99)
ORR, n (%) (97.5% CI)	31 (32) (21.7–43.6)	35 (35) (24.8–47.0)
sCR, n (%)	2 (2)	2 (2)
CR, n (%)	5 (5)	3 (3)
VGPR, n (%)	11 (11)	18 (18)
PR, n (%)	13 (13)	12 (12)
MR, n (%)	4 (4)	5 (5)
SD, n (%)	27 (28)	22 (22)
CBR, n (%) (95% CI)	35 (36) (26.6–46.5)	40 (40) (30.7–50.7)

*Best response as assessed by independent review committee using IMWG 2016 criteria.[8] 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. For response-rate analyses, patients with unknown or missing data were treated as non-responders. CBR: sCR+CR+VGPR+PR+MR; ORR: sCR+CR+VGPR+PR.

The median DoR estimate was 11.0 months (95% CI, 4.2–NR) in the 2.5-mg/kg group and 6.2 months (95% CI, 4.8–NR) in the 3.4-mg/kg group (**Figure 2**).

Median PFS was 2.8 months (95% CI, 1.6–3.6) in the 2.5-mg/kg group and 3.9 months (95% CI, 2.0–5.8) in the 3.4-mg/kg group.

Figure 2. Duration of response in either group

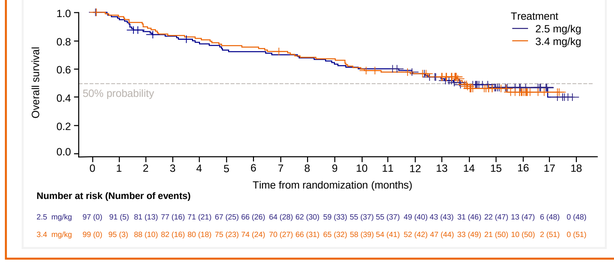


Number at risk (Number of events)

2.5 mg/kg	31 (0)	31 (0)	27 (3)	24 (5)	21 (6)	18 (9)	18 (9)	15 (11)	15 (11)	15 (11)	12 (11)	10 (12)	8 (13)	7 (14)	3 (15)	1 (15)	0 (15)
3.4 mg/kg	35 (0)	35 (0)	35 (0)	29 (5)	29 (5)	22 (12)	18 (15)	17 (14)	18 (14)	13 (18)	12 (18)	11 (19)	9 (19)	4 (19)	1 (19)	0 (19)	

Median OS estimate was 13.7 months (95% CI, 9.9–NR) in the 2.5-mg/kg group and 13.8 months (95% CI, 10.0–NR) in the 3.4-mg/kg group (**Figure 3**)

Figure 3. Overall survival in either group



Number at risk (Number of events)

2.5 mg/kg	97 (0)	91 (5)	81 (13)	77 (16)	71 (21)	67 (25)	66 (26)	64 (28)	62 (30)	59 (33)	55 (37)	55 (37)	49 (40)	43 (43)	31 (46)	22 (47)	13 (47)	6 (48)	0 (48)
3.4 mg/kg	99 (0)	95 (3)	88 (10)	82 (16)	80 (18)	75 (23)	74 (24)	70 (27)	66 (31)	65 (32)	58 (39)	54 (41)	52 (42)	47 (44)	33 (49)	21 (50)	10 (50)	2 (51)	0 (51)

Safety

AEs of any grade occurred in 93 (98%) and 99 (100%) patients in the 2.5-mg/kg and 3.4-mg/kg groups, respectively, with TRAEs in 84 (88%) and 94 (95%) patients.

In the 2.5-mg/kg and 3.4-mg/kg groups, SAEs occurred in 40 (42%) and 47 (47%) patients, of which 11 (12%) and 20 (20%) were study-treatment related; 3 (3%) and 9 (9%) were fatal (1 [1%] and 2 [2%] study-treatment-related fatal events).

Grade≥3 AEs were reported in 83 (84%) and 82 (84%) of patients in 2.5-mg/kg and 3.4-mg/kg groups, respectively, with the most common being keratopathy (MECs; changes in the corneal epithelium observed on eye examination with or without symptoms), thrombocytopenia, and anaemia (**Table 2**).

Table 2. AEs ≥Grade 3 occurring in ≥5% of patients in either group

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)
Anemia	20 (21)	27 (27)
Thrombocytopenia‡	21 (22)	32 (32)
Lymphocyte count decreased	12 (13)	7 (7)
Neutropenia§	10 (11)	17 (17)
Hypercalcemia	7 (7)	3 (3)
Pneumonia	7 (7)	13 (13)
GGT increased	3 (3)	9 (9)
Hypertension	4 (4)	7 (7)
AST increased	2 (2)	8 (8)
Fatigue	2 (2)	5 (5)

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 MECs) 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 haemorrhage (2 cases within the 3.4-mg/kg group only). §Includes preferred terms neutropenia, febrile neutropenia, and neutrophil count decreased.

AESI

Thrombocytopenia and IRR

Thrombocytopenia was reported in 36 (38%) and 56 (57%; including 2 Grade 5 events in the 3.4-mg/kg group only) patients, and IRRs in 20 (21%) and 16 (16%) patients in the 2.5-mg/kg and 3.4-mg/kg groups, respectively.

Keratopathy (MECs)

The most common AE, keratopathy (MECs), defined as changes to the superficial corneal epithelium, occurred in 68 (72%) patients in the 2.5-mg/kg group and 76 (77%) of patients in the 3.4-mg/kg group.

- As of this analysis, 77% and 73% of patients with keratopathy (MECs) had recovered from their first event, and 48% and 47% had recovered from their last event. The median time to onset of first MEC event was 37.0 and 22.5 days in the 2.5-mg/kg and 3.4-mg/kg groups, respectively, with the majority (69% and 77%) of patients experiencing their first event by dose 4.

Patients may experience symptoms of dry eye (any grade: 15% and 25% in the 2.5 and 3.4-mg/kg groups), blurred vision (any grade: 25% and 33% in the 2.5 and 3.4-mg/kg groups), and changes in visual acuity.

- Grade 3/4 symptoms were less common: dry eye (1% and 0% in the 2.5 and 3.4-mg/kg groups) and blurred vision (4% in both groups).
- 18% (17/95) and 20% (20/99) in the 2.5-mg/kg and 3.4-mg/kg groups, respectively, had a BCVA decline to 20/50 or worse in their better-seeing eye at least once during or after the treatment period.
- The median time to onset of first BCVA change was 66.0 and 83.5 days in the 2.5-mg/kg and 3.4-mg/kg groups, respectively.
- First events resolved in 82% and 100% patients in a median of 21.5 or 23.5 days in 2.5-mg/kg and 3.4-mg/kg groups, respectively; dose delays/reductions were used in 41% and 60%, respectively.
- As of the last follow-up, 82% (14/17) and 90% (18/20) of patients recovered from any BCVA change (BCVA better than 20/50). No permanent loss of vision has been reported to date.

Dose Modifications

Dose delays and reductions due to AEs were common (54% and 62% in the 2.5- and 3.4-mg/kg groups, respectively, **Table 3**). 9% and 12% of patients discontinued due to an AE, in the 2.5- and 3.4-mg/kg groups, respectively. Of these, 3% of patients (3 each in the 2.5- and 3.4-mg/kg groups, respectively) discontinued treatment due to corneal events (keratopathy [MECs], change in BCVA, or patient-reported AE/symptom).

Table 3. Dose delays, reductions and discontinuations due to AEs

n (%)	Belamaf 2.5 mg/kg (N=95)	Belamaf 3.4 mg/kg (N=99)
AEs leading to dose delays	51 (54)	61 (62)
Dose delays due to keratopathy (MECs), n (%)	45 (47)	52 (53)
AEs leading to dose reductions	33 (35)	44 (44)
Dose reductions due to keratopathy (MECs), n (%)	24 (25)	30 (30)
AEs leading to permanent treatment discontinuation	9 (9)	12 (12)
Discontinuations due to keratopathy (MECs), n (%)	1 (1)	3 (3)
Discontinuations due to patient-reported AEs/symptoms, n (%)	2 (2)*	0

*Blurred vision or change in BCVA (n=1 each).

In a post-hoc analysis (**Figure 4**), approximately half of responders (16/31) in 2.5-mg/kg group had a treatment hold for ≥3 cycles and were able to re-start. Most (88%) maintained or improved their response category during the dose delay.

Figure 4. Confirmed by timepoint in patients with dose delays >63 days (13-month follow-up; post-hoc analysis; 2.5 mg/kg group)

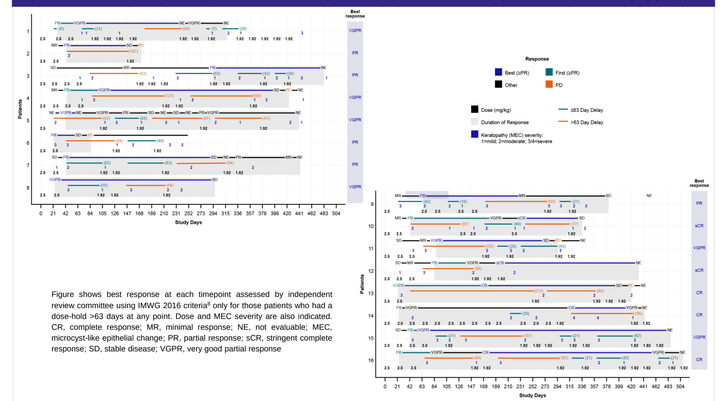


Figure shows best response at each timepoint assessed by independent review committee using IMWG 2016 criteria[8] only for those patients who had a dose-hold >63 days at any point. Dose and MEC severity are also indicated. CR, complete response; MR, minimal response; NE, not evaluable; MEC, microcyst-like epithelial change; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response

Discussion and Conclusions

Single-agent belamaf represents an important new treatment option for patients with heavily pre-treated RRMM, whose depth and duration of responses to treatment are known to diminish with each line of therapy (median PFS: 3.4 months; median OS: 9.3 months).[1-4]

In this trial, we show deep and durable responses with single-agent belamaf were sustained with longer follow-up in this RRMM population.

- In the 2.5-mg/kg group, the median DoR estimate was 11 months and median OS estimate was 13.7 months.
- In the 3.4-mg/kg group, the median DoR estimate was 6.2 months and the median OS estimate was 13.8 months.
- The estimated 1-year survival was 57% in both groups.

No new safety signals were identified with longer term follow-up with single-agent belamaf.

- Though keratopathy (MECs) observed on eye examinations was common, few patients (3 in each of the 2.5 and 3.4 mg/kg groups, respectively) discontinued treatment due to corneal events, suggesting that they were adequately managed with dose modifications.
  - Patient-reported symptoms (dry eye and blurred vision) were mainly Grade 1/2.
  - Changes in BCVA were manageable with dose modifications and resolved around of the time of the next eye examination (conducted ~every 21 days). No permanent loss of vision has been reported to date.

Although dose modifications (delays or reduction) to manage AEs were common, there was no impact on patients experiencing clinically meaningful deep and durable responses.

Abbreviations

3L, third line;
AE, adverse event;
AESI, adverse event of special interest;
ASCT, autologous-stem cell transplant;
AST, aspartate aminotransferase;
BCMA, B-cell maturation antigen;
BCVA, best-corrected visual acuity; belamaf, belantamab mafodotin;
CBR, clinical benefit rate;
CI, confidence interval;
CR, complete response;
DoR, duration of response;
DREAMM, DRiving Excellence in Approaches to Multiple Myeloma;
ECOG PS, Eastern Cooperative Oncology Group performance status;
FLC, free-light chain;
GGT, gamma-glutamyltransferase;
IMWG, International Myeloma Working Group;
IQR, interquartile range;
IRR, infusion-related reaction;
mAb, monoclonal antibody;
MEC, microcyst-like epithelial change;
MR, minimal response;
NE, not evaluable;
NR, not reached;
ORR, overall response rate;
OS, overall survival;
PFS, progression-free survival;
PI, proteasome inhibitor;
PR, partial response;
RRMM, relapsed/refractory multiple myeloma;
SAE, serious adverse event;
sCR, stringent complete response;
SD, stable disease;
TRAE, treatment-related adverse event;
TTP, time to progression;
TTBR, time to best response;
TTR, time to response;
VGPR, very good partial response

Disclosures

SL has received grant funding and personal fees from Celgene and Takeda, and personal fees from Novartis, Bristol-Myers Squibb, GlaxoSmithKline, Amgen, Merck, and Janssen. **HCL** has received grant funding and personal fees from Amgen, Celgene, Janssen, and Takeda; personal fees from GlaxoSmithKline and Sanofi, and grant funding from Daiichi Sankyo. **AB** received consulting fees from Amgen. **ST** received consulting fees from Celgene, Amgen GlaxoSmithKline; honoraria from Celgene, Janssen, Takeda, Sanofi, Karyopharm, and Amgen Canada; and research funding from Celgene, Janssen, Amgen, GlaxoSmithKline, and Genentech. **AKN** received consulting fees from Amgen, Janssen Oncology, Celgene, Spectrum Pharmaceuticals, Bristol-Myers Squibb, GlaxoSmithKline, Takeda, Oncopeptides, and Karyopharm Therapeutics; personal fees from GlaxoSmithKline; and research funding from Amgen, Janssen Oncology and Takeda. **AC** received consulting fees from Celgene, Novartis, Amgen, Janssen Oncology, Seattle Genetics, Bristol-Myers Squibb, Karyopharm Therapeutics, Genzyme, Oncopeptides, Takeda, Antengene, GlaxoSmithKline, and Secura Bio; and research funding from Celgene, Novartis, Janssen, Pharmacyclics, Amgen, Seattle Genetics, and Takeda. **A-OA** declares no competing interests. **NC** received research funding from Cellectar. **DS** received consulting fees, honoraria, and personal fees from Janssen. **AS** received consulting fees from GlaxoSmithKline, Janssen, and Karyopharm Therapeutics; research funding from GlaxoSmithKline, Janssen, Bristol-Myers Squibb, and Celgene; and personal fees from GlaxoSmithKline and Janssen. **KW** received consulting fees/honoraria from Amgen, Adaptive, Bristol-Myers Squibb, Celgene, Janssen, GlaxoSmithKline, Karyopharm, Takeda and Sanofi; and research funding from Amgen, Celgene, Sanofi, and Janssen. **PMV** has received personal fees from Adaptive Biotechnologies, Bristol-Myers Squibb /Celgene, Janssen, Novartis, Oncopeptides, and TeneoBio. **AH**, **EZ**, **JB**, **TP**, **RCJ**, and **JO** are employees of and hold stocks and shares in GlaxoSmithKline. **IG** is an employee of and holds stocks/shares in GlaxoSmithKline and holds stocks/shares in Novartis. **ADC** has received grant funding from GlaxoSmithKline, Bristol-Myers Squibb, and Novartis; personal fees from Janssen, Takeda, Oncopeptides, Kite Pharma, and Seattle Genetics, and personal fees and other association with GlaxoSmithKline and Celgene.

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