A phase 3, open-label, randomized study to evaluate the efficacy and safety of single-agent belantamab mafodotin (belamaf) compared to pomalidomide plus low-dose dexamethasone (Pd) in patients (pts) with relapsed/refractory multiple myeloma (RRMM) (DREAMM-3)

Poster No. MM-509

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Aims

Belantamab mafodotin (belamaf), a first-in-class humanized antibody-drug conjugate targeting B-cell maturation antigen (BCMA), induces cell death by direct cell killing and immune-mediated mechanisms.[1-3]

The doublet of immunomodulatory agent pomalidomide in combination with low-dose dexamethasone (Pd) is approved for patients with relapsed or refractory multiple myeloma (RRMM) in most countries.

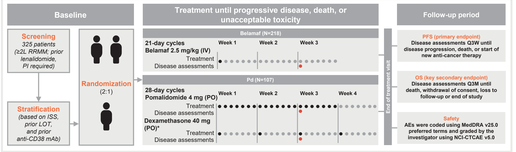
DREAMM-3 (NCT04162210; GSK study 207495) was the first randomized controlled trial to compare belamaf with a standard-of-care regimen.

Objective

DREAMM-3 was a superiority study designed to evaluate the efficacy and safety of single-agent belamaf vs a doublet (Pd) in adult patients with RRMM at second relapse or later.

Methods

Figure 1. DREAMM-3 study design



*Dexamethasone dose for those >75 years of age was 20 mg. 2L, second-line; AEs, adverse events; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; ISS, International Staging System; IV, intravenous; LOT, lines of therapy; mAb, monoclonal antibody; MedDRA, Medical Dictionary for Regulatory Activities; Q3W, every three weeks; OS, overall survival; PFS, progression-free survival; PO, by mouth RRMM, relapsed/refractory multiple myeloma.

Results from the primary analysis were previously presented at the 2023 ASCO Annual Meeting (presentation no. 8007).[4]

Additional follow-up on efficacy was conducted 10 months after the primary analysis data cutoff to further evaluate PFS, DoR, and OS of belamaf relative to Pd in all randomized patients; these analyses are considered descriptive only, and no formal statistical testing were planned.

All safety analyses were conducted at the primary analysis data cutoff only.

Results

Table 1. Patient baseline demographics and disease characteristics
(ITT population)

Characteristic, n (%)	Belamaf N=218	Pd N=107
Age, median (range)	68 (43–86)	68 (38–90)
≥75 years	47 (22)	23 (21)
Male	118 (54)	66 (62)
High-level race		
White	162 (76)	84 (81)
Asian	47 (22)	19 (18)
Black or African American	3 (1)	1 (<1)
ISS stage at screening		
Stage I/II	165 (76)	78 (73)
Stage III	52 (24)	28 (26)
Extramedullary disease, yes	39 (18)	19 (18)
High-risk cytogenetics*	57 (26)	34 (32)
Renal impairment per eGFR (mL/min/1.73m²)†		
Mild to moderate (≥30 to <90)	159 (73)	83 (78)
Prior lines of therapy, median (range)‡	4 (2–12)	3 (2–13)
≤3 lines	108 (50)	54 (50)
>3 lines	110 (50)	53 (50)
≥6 lines	33 (15)	8 (7)
Prior daratumumab exposed, n (%)	88 (40)	41 (38)
Refractory to prior therapy		
Anti-CD38 mAb + PI + IMiD	46 (21)	22 (21)

*High-risk cytogenetics were defined as the following: t(4;14), t(14;16) or 17p13del. †Five patients met the inclusion criteria at screening visit (eGFR <30 mL/min/1.73 m²) but had eGFR <30 mL/min/1.73 m² at Cycle 1 visit. ‡The number of prior lines of therapy is derived as the number of prior anti-cancer regimens received by a patient as reported on the electronic case report form. Combination therapy containing multiple components was counted as one regimen.
eGFR, estimated glomerular filtration rate; IMiD, immunomodulatory drug; ISS, International Staging System; mAb, monoclonal antibody; Pd, pomalidomide plus dexamethasone; PI, proteasome inhibitor.

Table 2. Patient disposition at primary analysis
(ITT population)

	Belamaf N=218	Pd N=107
Median follow-up, months (range)	11.5 (0.6–24.2)	10.8 (0.0–26.4)
Subject status, n (%)		
Ongoing	113 (52)	59 (55)
On study treatment	56 (26)	22 (21)
In follow-up	57 (26)	37 (35)
Died	83 (38)*	38 (37)*
Progressive disease†	57 (26)*	22 (22)*
Other	26 (12)*	16 (16)*
Withdrawn from the study	21 (10)	10 (9)
Reason for study withdrawal		
Withdrawal by subject	17 (8)	9 (8)
Burden of procedure	6 (3)	6 (6)
Other	13 (6)	5 (5)
Lost to follow-up	4 (2)	1 (<1)

*Proportions were calculated based on the safety population of n=217 for belamaf, and n=102 for Pd. †All deaths reported as due to unequivocally or equivocally due to disease under progression or multiple myeloma.

Median follow-up was 11.5 months for belamaf and 10.8 months for Pd at primary analysis.

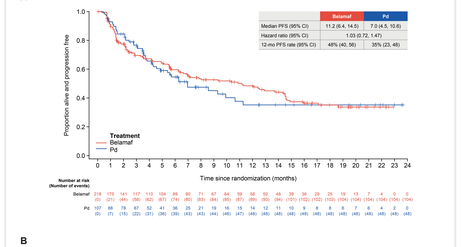
Median PFS was longer for belamaf than for Pd at the primary analysis, but PFS hazard ratio (HR) did not reach statistical significance (**Figure 2A**).

- Kaplan–Meier curves cross over at ~4 months.

Figure 2B shows the KM estimate for PFS with an additional 10 months of follow-up and increased data maturity.

- HR decreased from 1.03 (95% CI 0.72, 1.47) to 0.90 (95% CI 0.65, 1.24) at 10-mo follow-up.

Figure 2. Kaplan–Meier analysis of progression-free survival at A) the primary analysis and B) 10 months of additional follow-up
(ITT population)



Overall response rate (ORR) was 41% for belamaf vs 36% for Pd at primary analysis; as expected, this did not change with additional follow-up.

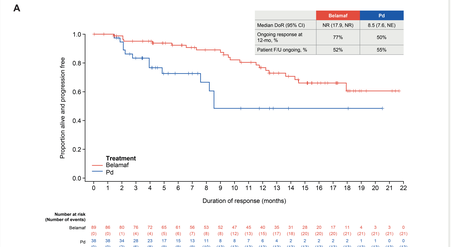
Deeper responses were seen with belamaf vs Pd (≥VGPR: 25% vs 8%; ≥CR: 10% vs 3%).

Minimal residual disease negativity rate (≥VGPR) was higher with belamaf vs Pd (7% vs 0%).

Median duration of response (DoR) was longer for belamaf than for Pd at primary analysis; Kaplan–Meier curves show clear and early separation (**Figure 3A**).

With 10 months of additional follow-up, belamaf demonstrated ~2.5-fold improvement in median DoR compared with Pd (Figure 3B).

Figure 3. Kaplan–Meier analysis of duration of response at A) the primary analysis and B) 10 months of additional follow-up
(ITT population)



DoR was a secondary endpoint and was not tested for statistical significance.

Median PFS on subsequent line of therapy (PFS2) was longer for belamaf compared with Pd at the primary analysis: belamaf **18.7** months (95% CI: 14.5, NR), Pd: **12.7** months (95% CI: 9.3, 21.1).

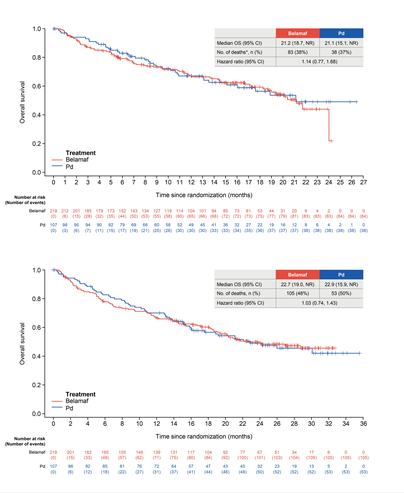
- Data on PFS2 were less than 50% mature at primary analysis.

Median OS was similar between arms at the primary analysis and at 10 months of additional follow-up (**Figure 4**).

However, with an additional 10 months of follow-up, the HR for OS decreased from 1.14 to 1.03 (**Figure 4B**).

- OS data maturity went from 37.5% to 48.6%

Figure 4. Kaplan–Meier analysis of overall survival at A) the primary analysis and at B) 10 months of additional follow-up
(ITT population)



*Proportions were calculated based on the safety population of n=217 for belamaf, and n=102 for Pd.
CI, confidence interval; NR, not reached OS, overall survival; Pd, pomalidomide plus dexamethasone.

Table 3. Incidence of adverse events
(Safety population; primary analysis)

	Belamaf N=217	Pd N=102
Any AE, n (%)	211 (97)	95 (93)
AEs related to study treatment	182 (84)	78 (76)
Grade 3 or 4 AE*	164 (76)	71 (70)
Grade 3 or 4 AEs related to study treatment	123 (57)	55 (54)
Any SAE, n (%)	94 (43)	40 (39)
SAEs related to study treatment	25 (12)	12 (12)
Fatal SAEs†	16 (7)	11 (11)
Fatal SAEs related to study treatment	0	1 (<1)
AEs leading to dose modification, n (%)		
AEs leading to dose interruption/delay of study treatment(s)	133 (61)	52 (51)
AEs leading to dose reduction of study treatment(s)	79 (36)	36 (35)
AEs leading to permanent discontinuation of study treatment(s)	33 (15)	17 (17)

*Maximum grades reported during event. †Fatal SAEs included sepsis/septic shock (n=6), cardiac arrest/failure (n=4), COVID-19/COVID-19 pneumonia (n=3), pneumonia (n=3), respiratory tract infection (n=2), plasma cell myeloma (n=2), subdural hematoma, pleural effusion, hemorrhagic stroke, anemia, AML, traffic accident, abdominal compartment syndrome (n=1 each). AE, adverse event; SAE, serious adverse event.

Incidence of AEs, SAEs, and Grade 3/4 events was similar between treatment arms at primary analysis.

Severe neutropenia and infections were more common with Pd, while severe thrombocytopenia was more common with belamaf at primary analysis.

Table 4. Incidence of hematologic AEs, infections, and any Grade 3 or higher events
(Safety population; primary analysis)

n (%)	Belamaf N=217	Pd N=102
Hematologic AEs	**117 (54)**	**58 (57)**
Neutropenia	24 (11)	39 (38)
Grade ≥3	18 (8)	34 (33)
Neutrophil count decreased	18 (8)	15 (15)
Grade ≥3	10 (5)	12 (12)
Thrombocytopenia	74 (34)	31 (30)
Grade ≥3	49 (23)	16 (16)
Platelet count decreased	29 (13)	12 (12)
Grade ≥3	20 (9)	6 (6)
Infections and infestations (≥10%)	**90 (41)**	**41 (40)**
COVID-19	28 (13)	12 (12)
Pneumonia	8 (4)	11 (11)
Grade 3 or higher (≥5%)	29 (13)	25 (25)
Pneumonia	6 (3)	9 (9)
COVID-19	5 (2)	4 (4)
COVID-19 pneumonia	2 (<1)	4 (4)
Febrile neutropenia	2 (<1)	5 (5)

At primary analysis, severe decreases in visual acuity were infrequent and resolved upon follow up.

Table 5. Bilateral worsening of Snellen scores (BCVA)
(Safety population; primary analysis)

Bilateral worsening, n (%)	Belamaf (N=217)	Pd (N=102)
20/50 or worse	38 (18)	1 (1)
20/200 or worse*	5 (2)	0
Bilateral worsening to 20/50 or worse	**Belamaf (N=38)**	**Pd (N=1)**
Time to first event onset, days, median (range)	62 (18–582)	84 (NA)
First event resolved†, n (% of patients)	36 (95)	1 (100)
Time to first event resolution, days, median (range)	40 (8–278)	85 (NA)

*At baseline, 1 patient had 20/20 in both eyes, 1 had 20/50 in both eyes, 1 had 20/100 in both eyes, and 2 patients had 20/100 in their worse eye. †Resolution was defined as returning to baseline level. BCVA, best corrected visual acuity; Pd, pomalidomide plus dexamethasone.

Ocular AESIs were predominantly mild-moderate and 81% were resolved/resolving at primary analysis.

Table 6. Incidence of ocular adverse events of special interest
(Safety population; primary analysis)

Ocular AESI*, n (%) (≥10% incidence)	Belamaf (N=217)			Pd (N=102)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Patients with any event	143 (66)	59 (27)	5 (2)	8 (8)	0	0
Events						
Vision blurred	86 (40)	9 (4)	2 (<1)	2 (2)	0	0
Visual acuity reduced	41 (19)	18 (8)	1 (<1)	1 (<1)	0	0
Dry eye	61 (28)	9 (4)	0	2 (2)	0	0
Foreign body sensation in eyes	57 (26)	2 (<1)	0	2 (2)	0	0
Eye irritation	50 (23)	2 (<1)	0	1 (<1)	0	0
Photophobia	46 (21)	1 (<1)	0	1 (<1)	0	0
Eye pain	35 (16)	1 (<1)	0	0	0	0
Keratopathy†	26 (12)	8 (4)	1 (<1)	1 (<1)	0	0
Punctate keratitis	23 (11)	8 (4)	0	0	0	0

*AEs were coded by MedRA v25.0 and graded by the investigator using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. Individual patients could have multiple events reported. †The keratopathy reported in DREAMM-3 appears lower than previously reported due to a different approach to data collection and reporting. When compared with DREAMM-2 using the same methodology, the frequency and severity of keratopathy (defined as changes on ocular exam) was very similar.
AESI, adverse event of special interest; Pd, pomalidomide plus dexamethasone.

Conclusions

Single-agent belamaf demonstrated longer median PFS and deeper and more durable responses compared with Pd; however, PFS HR did not reach statistical significance.

OS was similar between single-agent belamaf and Pd.

No new safety signals were observed with single-agent belamaf; ocular toxicity was successfully managed with dose modifications. Severe decreases in visual acuity were infrequent and almost all resolved during follow-up.

Significantly lower rates of neutropenia and Grade 3 or higher infections were observed with belamaf compared with Pd.

While the DREAMM-3 study did not meet its primary objective of demonstrating PFS superiority, single-agent belamaf appears to show clinically meaningful improvement in durability of response compared to a doublet regimen in RRMM.

An additional 10 months of follow-up demonstrated an improved HR for PFS from 1.03 to 0.90 and OS from 1.14 to 1.03. In addition, median DoR was 25.6 months for belamaf vs 10.4 for Pd, suggesting a ~2.5-fold improvement in estimated DoR.

Disclosures

MAD has received fees from Advisory Boards from AbbVie, Amgen, Bristol Myers Squibb, BeiGene, GSK, Janssen, Karyopharm Therapeutics, Pharmacyclics, Pfizer, Sanofi, and Takeda. **VTMH** has received fees for consulting from AbbVie, Amgen, BMS, Celgene, Janssen, Sanofi, and Takeda. **AR** has received honoraria from Roche, Pfizer, AbbVie, Swixx, SOBI, and Novartis; consulting or advisory fees from Roche, Swixx, SOBI. **SD** has received honoraria from Amgen, GSK, Janssen, and Takeda. **GM** has received honoraria from AbbVie, Amgen, Celgene, Janssen, BMS, Takeda, Roche, and Richter; has received consulting or advisory fees from AbbVie, Amgen, Celgene, Janssen, BMS, Takeda, Roche; research funding from AbbVie; and fees for travel, accommodations, and expenses from BMS, Janssen, and Takeda. **TM** has received fees for participation on a Data Safety Monitoring Board or Advisory Board from AbbVie, BMS, Janssen, Novartis, Pfizer, and Takeda. **JL** has no conflicts to report. **MC** has received speaker's bureau participation fees from Sanofi, BMS, and Janssen; and fees for travel, accommodations, and expenses Sanofi, BMS, and Janssen. **MM** has no conflicts to report. **NS** is an employee of GSK and holds stocks and shares in GSK, Pfizer, and BMS. **ML** is an employee of GSK and holds stocks and shares in GSK and AstraZeneca. **AM** is an employee of and holds stocks and shares in GSK. **WH** was an employee of GSK at the time this analysis was completed and holds stocks and shares in GSK. **SB** is an employee of and holds stocks and shares in GSK. **BC** is an employee of and holds stocks and shares in GSK. **JB** is an employee of and holds stocks and shares in GSK. **JO** is an employee of and holds stocks, patents, and shares in GSK. **KW** has received honoraria from AbbVie, Amgen, Adaptive Biotech, AstraZeneca, BMS/Celgene, Janssen, GSK, Karyopharm Therapeutics, Novartis, Oncopeptides, Pfizer, Roche, Sanofi, Stemline, and Takeda; consulting or advisory fees from AbbVie, Amgen, Adaptive Biotech, BMS/Celgene, Janssen, GSK, Karyopharm Therapeutics, Oncopeptides, Pfizer, Roche, Sanofi, and Takeda; and research funding from AbbVie, Amgen, BMS/Celgene, Janssen, GSK, and Sanofi.

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