Safety and Clinical Activity of Belantamab Mafodotin With Pembrolizumab in Patients With Relapsed/Refractory Multiple Myeloma (RRMM): DREAMM-4 Study

Poster No. 442

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Background

Belantamab mafodotin (belamaf), a B-cell maturation antigen (BCMA)-targeting antibody-drug conjugate, has a multimodal mechanism of action that eliminates multiple myeloma (MM) cells via direct cytotoxicity as well as by a systemic anti-MM tumor immune response[1-3]

Belamaf 2.5 mg/kg Q3W is the only BCMA-targeted ADC monotherapy approved for the treatment of patients with triple class refractory/exposed MM[4,5]

In the pivotal Phase II DREAMM-2 study, single-agent belamaf (2.5 mg/kg Q3W) demonstrated deep and durable responses (ORR 32%, median duration of response of 11.0 months, and median overall survival of 13.7 months), in patients with RRMM.[6,7]

The hypothesis underlying this study was that the multimodal mechanism of belamaf may be augmented by pembrolizumab (pembro), an anti-PD-1 antibody that can facilitate activation of an anti-tumor immune response[8], to produce a synergistic anti-myeloma effect.

Aim

The DREAMM-4 study (NCT03848845) assessed the safety and clinical activity of belamaf in combination with pembro in patients with heavily pre-treated RRMM.

Methods

This was a Phase I/II, single-arm, open-label study of adults with RRMM who had received ≥3 lines of therapy (LOT), including anti-CD38 monoclonal antibody, proteasome inhibitor, and immunomodulatory agent.

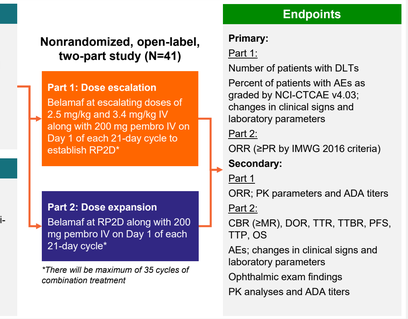
Part 1 was a dose-escalation phase that established the dose of belamaf 2.5 mg/kg with pembro 200 mg, both given IV Q3W for up to 35 cycles; this dose was used for the Part 2 expansion cohort. Patients from Part 1 and Part 2 who received belamaf at the established dose of 2.5 mg/kg were combined for analysis, as defined in the protocol.

The eligibility criteria and endpoints for each Part are represented in **Figure 1**.

- The endpoint of ORR was assessed by the investigator and defined as the percentage (with 95% CI) of patients with a confirmed partial response (PR) or better according to the International Myeloma Working Group (IMWG) Response Criteria.[9]
- Adverse events, including keratopathy, were graded by the investigator according to the NCI-CTCAE version 4.03; coding was based on the standard MedDRA.
- Blood samples were collected for assessing plasma pharmacokinetics (PK) of belamaf.

Data in Part 1 were analyzed using descriptive methods; no statistical hypotheses were tested. The null hypothesis evaluated in the Part 2 expansion cohort was ORR ≤40%, while the alternative hypothesis was ORR ≥60%.

Figure 1. DREAMM-4 study design



Results

Patient disposition

This primary analysis of all treated patients who received belamaf 2.5 mg/kg + pembro 200 mg (as of Oct 17, 2021) included 34 patients: 6 patients from Part 1 and 28 patients from Part 2.

In both parts, median prior LOT was 5 (range 3–13); 10 patients (29%) had high-risk cytogenetics, 9 (26%) had extramedullary disease, and 14 (41%) were triple-class refractory (**Table 1**).

The median dose intensity of belamaf, reflecting dose modifications such as dose interruptions/delays and dose reductions, was slightly below the target dose at 2.304 mg/kg per 3 weeks; median pembro dose intensity was 200 mg per 3 weeks, consistent with the assigned dose.

Table 1. Patient baseline characteristics

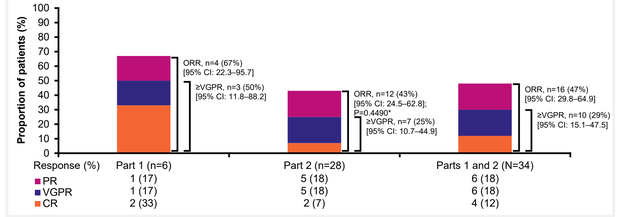
Characteristic	Part 1 (n=6)	Part 2 (n=28)	Parts 1 and 2 (N=34)
Age, median (range), years	72.5 (50–77)	60.5 (40–81)	61.0 (40–81)
Sex, n (%)			
Male	1 (17)	18 (64)	19 (56)
Female	5 (83)	10 (36)	15 (44)
Race, n (%)			
White	5 (83)	23 (82)	28 (82)
Black/African American	1 (17)	4 (14)	5 (15)
Asian	0	1 (4)	1 (3)
ISS disease stage, n (%)			
Stage I	2 (33)	7 (25)	9 (26)
Stage II	2 (33)	11 (39)	13 (38)
Stage III	1 (17)	7 (25)	8 (24)
Unknown	1 (17)	3 (11)	4 (12)
Cytogenetic abnormalities, n (%)			
High risk*	3 (50)	7 (25)	10 (29)
Other	3 (50)	21 (75)	24 (71)
Myeloma immunoglobulin, n (%)			
IgA	1 (17)	8 (29)	9 (26)
IgG	5 (83)	16 (57)	21 (62)
None	0	4 (14)	4 (12)
Extramedullary disease, n (%)			
Yes	0	9 (32)	9 (26)
Duration of follow-up, median (IQR)	15.69 (7.10–23.49)	14.65 (7.15–15.95)	14.65 (7.10–16.00)
Median number of prior LOT (range)	7.5 (3–13)	5.0 (3–12)	5.0 (3–13)
Triple-class† refractory, n (%)	4 (67)	10 (36)	14 (41)
Median belamaf dose intensity, mg/kg/3 weeks (range)	1.534 (1.08–2.48)	2.411 (0.42–2.51)	2.304 (0.42–2.51)
Median pembro dose intensity, mg/3 weeks (range)	131.9 (106–200)	200.0 (41–200)	200.0 (41–200)

*High-risk cytogenetics were defined as the presence of one or more of: t(4;14), t(14;16), 17p13del. †Refractory to anti-CD28 monoclonal antibody, proteasome inhibitor, and immunomodulatory agent.

Efficacy outcomes

In Parts 1 and 2 combined, the ORR was 47%, with most responses (10/16 patients) ≥VGPR (**Figure 2**).

Figure 2. Best response as assessed by investigator using IMWG 2016 criteria



*P-value is from a one-sided test to disprove the null hypothesis (ORR ≤40%) using the Exact method.

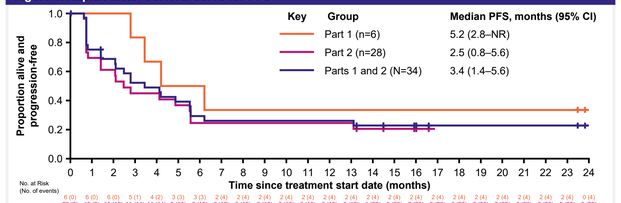
Time-to-event outcomes of DOR and TTR are shown in **Table 2**.

PFS is shown as a Kaplan-Meier analysis in **Figure 3**.

Table 2: Time-to-event outcomes

Outcome, reported in months	Part 1 (n=6)	Part 2 (n=28)	Parts 1 and 2 (N=34)
Duration of response, median (95% CI)	NR (2.1–NR)	7.6 (1.4–NR)	8.0 (2.1–NR)
Time to response, median (95% CI)	1.1 (0.6–2.9)	0.7 (0.7–1.4)	0.7 (0.7–1.4)

Figure 3. Kaplan-Meier survival curve for PFS



Safety

Most patients had ≥1 AE (any grade: 97%; grade ≥3: 74%) and treatment-related AE (TRAE, any grade: 97%; grade ≥3: 65%; **Table 3**).

The three most common AEs were keratopathy, blurred vision, and thrombocytopenia, each with an incidence of ≥35% across Parts 1 and 2.

In all cohorts, AEs led to dose interruptions (65%) and dose reductions (32%), but no discontinuations.

- The most common (≥10%) AEs, per CTCAE, leading to dose interruptions were keratopathy (44%) and thrombocytopenia (12%).

Nine patients had a serious AE (SAE); 4 patients had ≥1 SAE related to study treatment.

- The most common (>5%) SAEs in both Parts were pneumonia (15%), infusion-related reaction (9%), infection (6%), and urinary tract infection (6%).
- Infusion-related reactions (9%) and pneumonia (6%) were considered treatment-related, plus one case of serious treatment-related platelet count decrease.
- There were no study deaths attributed to an AE.
- One patient had a treatment-related immune-related AE of grade 1 autoimmune hypothyroidism.

Table 3. Safety outcomes

Outcome, n (%)	Part 1 (n=6)	Part 2 (n=28)	Parts 1 and 2 (N=34)
Any AE, all grades	6 (100)	27 (96)	33 (97)
Any AE, grade ≥3	6 (100)	19 (68)	25 (74)
Most common (≥20% in Parts 1 and 2 combined) AEs, all grades			
Keratopathy	6 (100)	20 (71)	26 (76)
Vision blurred	3 (50)	10 (36)	13 (38)
Thrombocytopenia	3 (50)	9 (32)	12 (35)
Infusion-related reaction	3 (50)	8 (29)	11 (32)
Pyrexia	1 (17)	10 (36)	11 (32)
Nausea	3 (50)	7 (25)	10 (29)
Anemia	4 (67)	5 (18)	9 (26)
Dry eye	3 (50)	4 (14)	7 (21)
Any TRAE	6 (100)	27 (96)	33 (97)
Any SAE	4 (67)	5 (18)	9 (26)
Treatment-related SAE	1 (17)	3 (11)	4 (12)
AE leading to dose reduction	2 (33)	9 (32)	11 (32)
AE leading to dose interruption	5 (83)	17 (61)	22 (65)
AE leading to permanent discontinuation	0	0	0

Pharmacokinetics

Observed exposures of total monoclonal antibody (belantamab with or without MMAF) and cys-mcMMAF after administration of belamaf in combination with pembro after the first dose (**Table 4**) and at steady state (data not shown) were similar to those reported previously after monotherapy administration of belamaf.[10]

Table 4. Total monoclonal antibody and cys-mcMMAF pharmacokinetic parameter values at cycle 1

Parameter	Part 1 (n=6)		Part 2 (n=28)		Parts 1 and 2 (N=34)	
Total monoclonal antibody						
	n	Value	n	Value	n	Value
AUC(0-τ) (μg.h/mL)	3	6237 (18)	19	7949 (27)	22	7691 (27)
Cmax (μg/mL)	4	43.6 (7.1)	26	46.7 (23)	30	46.3 (22)
tmax (h)	4	1.10 (0.53–2.18)	26	0.945 (0.47–2.33)	30	0.945 (0.47–2.33)
Ctrough (μg/mL)	3	5.48 (37)	20	6.37 (60)	23	6.24 (57)
Cys-mcMMAF						
	n	Value	n	Value	n	Value
AUC(0-168) (ng.h/mL)	1	155.3	18	128.4 (71)	19	129.7 (69)
Cmax (ng/mL)	2	1.580 (30)	26	1.248 (112)	28	1.269 (106)
tmax (h)	2	13.51 (4.05–22.97)	26	23.58 (0.52–70.65)	28	23.54 (0.52–70.65)

Data presented as geometric mean (%CVb), except tmax, presented as median (range). %CVb = sqrt (exp (SD of log values^2) - 1) * 100.

Biomarkers

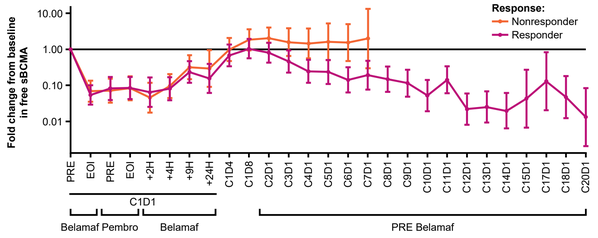
Preliminary soluble BCMA (sBCMA) data were consistent with belamaf monotherapy.

Data indicate that a moderate reduction in sBCMA level relative to baseline is observed in responders (≥PR), starting from Cycle 2 onward. In contrast, nonresponders had sBMCA levels that were persistently at or above baseline after Cycle 1 Day 1 (**Figure 4**).

- While responders' and nonresponders' baseline sBCMA levels followed a similar pattern of dropping at EOI and recovering to near-baseline by Cycle 1 Day 4, the data diverge as the pre-infusion sample taken at the beginning of subsequent cycles shows a steady decline in sBCMA levels in responders but not nonresponders.

Addition of pembro did not affect the sBCMA profile compared to belamaf monotherapy, as previously reported.[11]

Figure 4: Aggregate fold change (logarithmic scale) from baseline in free sBCMA by response status in the overall population (N=34)



Each datapoint represents the geometric mean of fold change from baseline. Whisker bars represent the 95% CI.

Conclusions

Belamaf + pembro demonstrated clinical activity and an appreciable ORR compared with the ORR of 32% reported in the DREAMM-2 study of belamaf monotherapy in patients with heavily pre-treated RRMM.[7]

- The ORR of 43% (95% CI: 24.5–62.8) in Part 2 was not statistically significant, and therefore the null hypothesis of ORR ≤40% was not rejected.

No new treatment-related AEs were identified; AE frequency and severity were similar to belamaf monotherapy.

There was no apparent effect of concomitant pembro administration on total monoclonal antibody and cys-mcMMAF pharmacokinetics, nor on the pattern of sBCMA levels over time, compared to belamaf monotherapy.

The results of this study help reinforce the body of research supporting belamaf use in patients with MM, and future studies will pursue other combination therapy options to enhance the efficacy-safety profile.

Abbreviations

ADA, anti-drug antibody; AE, adverse event; AUC, area under the curve; BCMA, B-cell maturation antigen; belamaf, belantamab mafodotin; C, cycle; CBR, clinical benefit rate (≥MR); CI, confidence interval; Cmax, maximum observed plasma concentration, CR, complete response; Ctrough, plasma concentration prior to next dose; cys-mcMMAF, cysteine maleimidocaproyl monomethyl auristatin F; D, day; DLT, dose-limiting toxicity; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EOI, end of infusion; IMWG, International Myeloma Working Group; ISS, International Staging System; IV, intravenous; LOT, line of therapy; mAb, monoclonal antibody; MedDRA, Medical Dictionary for Regulatory Activities; MM, multiple myeloma; MR, moderate response; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OS, overall survival; PD, progressive disease; PDL-1/2, programmed death-ligand 1/2; pembro, pembrolizumab; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; PRE, before infusion; Q3W, every 3 weeks; RP2D, recommended Phase II dose; RRMM, relapsed/refractory multiple myeloma; SAE, serious AE; sBCMA, soluble BCMA; SD, stable disease; tmax, time of Cmax; TRAE, treatment-related AE; TTBR, time to best response; TTP, time to progression; TTR, time to response; VGPR, very good partial response.

Disclosures

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References

1. Tai YT, et al. *Blood* 2014;123:3128–38.
2. Tai YT, Anderson KC. *Immunotherapy* 2015;7:1187.
3. Montes de Oca R et al. *Mol Cancer Ther* 2021;20:19411955.
4. US Food and Drug Administration. Belantamab mafodotin [Package Insert]. https://www.accessdata.fda.gov/drugsatfdadocs/label/2020/761158s000lbl.pdf [Accessed October 2021].
5. European Medicines Agency. Belantamab mafodotin SmPC. 2020. https://www.ema.europa.eu/en/medicines/human/EPAR/blenrep#authorisation-details-section [Accessed October 2021].
6. Lonial S, et al. *Lancet Oncol* 2020;21:207–21.
7. Lonial S, et al. *Cancer* 2021;127:4198–212.
8. Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA. Pembrolizumab prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s096lbl.pdf [Accessed May 2022].
9. Kumar S, et al. *Lancet Oncol* 2016;17:e328–e346.
10. Richardson PG, et al. *Blood Cancer J* 2020;10:106.
11. Nooka AK, et al. EHA 2020; June 11–14; virtual meeting. (poster No. EP955).

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