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The role of belantamab mafodotin for patients with relapsed and/or refractory multiple myeloma

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***Abstract*:** Belantamab mafodotin (belamaf) is a first-in-class anti-B-cell maturation antigen (BCMA) antibody–drug conjugate (ADC) that recently gained regulatory approval for the treatment of relapsed and/or refractory multiple myeloma (RRMM) patients who have received at least four prior therapies including an anti-CD38 monoclonal antibody (mAb), a proteasome inhibitor (PI), and an immunomodulatory drug (IMiD). As the first BCMA-targeted therapy to be approved in multiple myeloma along with its "off-the-shelf" outpatient administration, belamaf addresses a significant unmet need in RRMM that is refractory to IMiD, PI, and anti-CD38 mAb therapy, otherwise known as triple-class refractory myeloma. Belamaf is also associated with frequent corneal ocular adverse events, which represents a unique toxicity in multiple myeloma therapeutics, and its administration requires a multidisciplinary approach with oncologists and eye care specialists to safely and effectively manage patients on belamaf therapy. In this review, we discuss the preclinical and clinical data leading to the regulatory approval of belamaf, the monitoring and mitigation strategies of corneal ocular adverse events, and its current and future role in the RRMM treatment landscape.

Keywords: antibody–drug conjugate (ADC), B-cell maturation antigen (BCMA), belantamab mafodotin, multiple myeloma

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Introduction

Multiple myeloma (MM) accounts for 1.8% of new cancer diagnoses and 2.1% of all cancer-related deaths in the United States.[1] The development of multiple novel treatment options over the last two decades has led to improved survival for patients, but despite these advances, MM remains an incurable, though highly treatable, malignancy.[2–4] Many of these initial advancements in MM outcomes were the result of the incorporation of agents such as immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) into the backbones of MM therapeutic regimens both in the newly diagnosed and relapsed and/or refractory MM (RRMM) setting.[5,6] Subsequently, the development of monoclonal antibodies (mAb) targeting antigens on the surface of plasma cells such as CD38 has led to a new revolution in MM treatments with even further improvement in outcomes.[5,6] Despite these advances, drug resistance remains an inevitable challenge that most patients will face at some point in their treatment course. In particular, patients who are refractory to PIs, IMiDs, and anti-CD38 mAbs, otherwise known as triple-class refractory MM, have poor prognosis with a median overall survival of less than 1 year.[7] Therefore, efficacious and well-tolerated therapeutic options for the treatment of RRMM remains an unmet need.

B-cell maturation antigen (BCMA) has emerged as an attractive target for the treatment of MM in recent years. Various novel therapeutic approaches targeting BCMA, such as chimeric antigen receptor-modified T cells (CAR-Ts), bispecific antibody

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T-cell engagers (TCEs), and antibody–drug conjugates (ADCs), have demonstrated encouraging early efficacy in clinical trials.[8] Herein, we will discuss belantamab mafodotin (GSK2857916, belamaf), the first-in-class ADC and the first BCMA-targeted therapy that recently gained regulatory approval for RRMM patients who have received at least four prior therapies including an anti-CD38 mAb, a PI, and an IMiD. In this review, we discuss the preclinical and clinical data leading to the regulatory approval of belamaf, the monitoring and mitigation strategies of corneal ocular adverse events associated with belamaf, and its current and future role in the RRMM treatment landscape.

Preclinical data

The role of BCMA in multiple myeloma

BCMA, also known as CD269 and TNFRSF17, is a tumor necrosis factor transmembrane receptor that plays a critical role in B-cell maturation and is selectively induced during the differentiation of B cells to plasma cells.[8–12] BCMA enhances the survival of plasmablasts and plasma cells and therefore augments humoral immunity; however, while BCMA is required for optimal plasma cell bone marrow survival, it is generally not critical for B-cell homeostasis.[10,11] Murine and human models have demonstrated the association between MM and overexpression of BCMA, which makes it an attractive target for the treatment of MM.[8] B-cell activating factor (BAFF) and APRIL (a proliferation-inducing ligand), who are members of the TNF family that serves as ligands for BCMA, have also been associated with the proliferation of MM cells in the bone marrow.[8,13] Thus far, trials targeting BAFF and APRIL as part of the BAFF/APRIL/BCMA axis have been rather disappointing, and thus, BCMA has become a target of interest.[13] BCMA also has minimal expression in naïve B cells and non-hematopoietic cells, which is of particular importance from a therapeutic perspective.[8–12]

In addition to its uses therapeutically, BCMA is also of interest as a biomarker in MM. For example, soluble BCMA (sBCMA) levels are increased in MM patients and have been found to correlate with the tumor burden and survival, and could potentially be useful for monitoring response during MM treatment.[8,10,13] Moreover, sBCMA has a half-life of 24–26 hours, so changes in sBCMA levels may reflect changes in disease status faster than changes in paraprotein levels.[8,9] However, further investigation is needed into these uses of sBCMA in measuring response to therapy.

Targeting BCMA in multiple myeloma

Given the exclusive expression of BCMA on plasma cells, various novel therapeutic approaches, such as CAR-Ts, TCEs, and ADCs are currently being investigated in clinical trials with encouraging efficacy to target BCMA.[8] In general, ADCs can improve the efficacy of a naked mAb by combining a tumor antigen-specific mAb with a toxic payload that becomes internalized upon binding of the ADC to the tumor cell, ultimately resulting in cell death.[6,8,12–15] For example, belamaf is a first-in-class ADC that uses a protease-resistant linker to combine an afucosylated humanized IgG1 anti-BCMA mAb with monomethyl auristatin F (MMAF), which is an inhibitor of tubulin polymerization.[6,8,10–15] Preclinical studies demonstrated encouraging anti-MM activity of belamaf through several mechanisms of action including direct apoptosis through the ADC mechanism, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and immunogenic cell death.[10,11,14–16] Importantly, belamaf also demonstrated the ability to rapidly eliminate MM cells while sparing normal bone marrow stromal cells and immune effector cells when treated in co-culture.[10,11]

Clinical data

DREAMM-1

Encouraging preclinical data led to the evaluation of belamaf in the phase I DREAMM-1 trial, which was a first-in-human, open-label dose escalation (part 1) and expansion (part 2) study that evaluated the safety and preliminary efficacy of belamaf in RRMM. A total of 73 patients with RRMM with previous exposure to alkylator, PI, and IMiD therapy and who were refractory to their last line of treatment were enrolled on study. Of note, baseline BCMA expression levels was not assessed as part of eligibility criteria for trial enrollment. In an effort to mitigate corneal adverse events (AEs), which is a known toxicity of MMAF, steroid eye drops were administered four times daily for 4 days after each dose. Part 1 did

not identify a maximum tolerated dose as there were no dose-limiting toxic events observed. However, based on pharmacokinetic data, the lack of clinical activity in eight patients treated at the 2.5 mg/kg dose, the 100% overall response in three patients treated at 3.4 mg/kg, and poor tolerability of the 4.6 mg/kg dose, the recommended dose for part 2 of the study was established at 3.4 mg/kg every 21 days. Among 35 patients who were treated in part 2 of the study, the most common grade 3/4 AEs were thrombocytopenia (34%) and anemia (17%). Notability, 69% of patients experienced corneal AEs as per Common Terminology Criteria for Adverse Events v4.0 criteria, manifesting most commonly as blurred vision, dry eye, and photophobia, although the majority were grade 1–2 (54%). Dose reductions were required in 46% of patients and dose delays in 49% of patients due to corneal AEs. At the 3.4 mg/kg dose in part 2 of the study, the overall response rate (ORR) was 60%, with greater than 50% patients achieving a very good partial response (VGPR) or better. Among 13 triple-class (PI, IMiD, and anti-CD38 mAb) refractory patients, the ORR was 39%. Median duration of response was 14.3 months; median progression-free survival (PFS) was 12 months among all patients and 6.2 months in patients who were triple-class refractory.[14,15]

DREAMM-2

Based on the promising results of the DREAMM-1 study, the DREAMM-2 study was launched, which was a pivotal phase II registration study which enrolled RRMM patients who had progressed on at least three prior lines of therapy and were refractory to PIs and IMiDs and refractory or intolerant to an anti-CD38 mAb.[17] A total 196 patients enrolled on study and were randomized to either receive belamaf 2.5 mg/kg (cohort 1, $n = 97$ patients) or 3.4 mg/kg (cohort 2, $n = 99$ patients) every 3 weeks until disease progression or unacceptable toxicity. Patients had a median of seven (cohort 1) and six (cohort 2) prior lines of treatment, and 96% patients were triple-class refractory. Ophthalmic exams were performed at baseline and prior to each dose to monitor for ocular AEs. Corticosteroid eye drops and preservative-free artificial tears were prophylactically administered to mitigate the expected corneal toxicities from MMAF as noted in DREAMM-1. Of note, there was also an ocular substudy within the DREAMM-2 study with planned enrollment of 15 patients in each cohort to assess the utility of prophylactic steroid eye drops to mitigate keratopathy. In this substudy, patients self-administered prophylactic steroid eye drops in one eye in order to evaluate the benefit of this approach in mitigating ocular toxicity.

At the primary data cut-off, the ORR was 31% of patients in cohort 1 and 34% of patients in cohort 2 with a ⩾VGPR rate of 19% of cohort 1 and 20% in cohort 2. The median PFS was 2.9 in cohort 1 and 3.9 months in cohort 2. At a later 13-month follow-up data cut-off, median duration of response was reported to be 11 months in cohort 1 and 6.2 months in cohort 2. Median overall survival was 13.7 months and 13.8 months, respectively, in cohorts 1 and 2.[18] Although the ORR of 60% reported in the DREAMM-1 trial was substantially higher, the DREAMM-2 ORR was similar to the subset of triple-class refractory patients in the DREAMM-1 trial who had an ORR of 39%.[14,15]

The most common grade 1–2 AE was keratopathy, and the most common grade 3–4 AEs were keratopathy (cohort 1 27%/cohort 2 21%), thrombocytopenia (20%/33%), and anemia (20%/25%). Premedications were not mandated per protocol, and infusion-related reactions (IRRs) occurred in 21% of patients in cohort 1 and 16% of patients in cohort 2, although nearly all were limited to grade 1–2 in severity. Most IRRs were limited to the first dose. About 1/4 of patients treated on study did receive premedications to mitigate IRRs prior to the first dose of belamaf, although this did not proportionately decrease the incidence of IRRs in these patients compared with the overall study population.

AEs leading to dose delays were reported in 54% and 62% of patients in cohort 1 and cohort 2, respectively. AEs leading to dose reductions occurred in 29% in cohort 1 and 41% of patients in cohort 2, and AEs leading to treatment discontinuation occurred in 8% and 10% in the respective cohorts. The most common reason for treatment delays (cohort 1 47%/cohort 2 48%), dose reductions (23%/27%), and treatment discontinuations (1%/3%) was related to keratopathy. Treatment delays due to keratopathy began at approximately 4 weeks in each cohort, and median time to treatment re-initiation was 83 days in cohort 1 and 63 days in cohort 2.

In the ocular substudy, median time to keratopathy was no different with or without prophylactic corticosteroid eye drops, and therefore they are no longer recommended with belamaf administration. The 2.5 mg/kg dose (cohort 1) was selected as the recommended treatment dose for future studies and submission for regulatory approval given similar efficacy and a more favorable safety profile compared with the 3.4 mg/kg dose (cohort 2). The efficacy and safety data of the DREAMM-2 study recently led to the regulatory approval of belamaf for the treatment of RRMM patients who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a PI, and an IMiD.

DREAMM-6

DREAMM-6 is an ongoing, two-arm study evaluating the safety, tolerability, and efficacy of belamaf in combination with lenalidomide/dexamethasone (Rd) (Arm A) and bortezomib/dexamethasone (Vd) (Arm B) in RRMM with at least one line of prior therapy. Preliminary data for belamaf in combination with Vd (Arm B) was recently reported.[19] Arm B of DREAMM-6 consisted of part 1 (dose escalation) and part 2 (dose expansion) evaluating belamaf (2.5 and 3.4 mg/kg) administered as single dose on day 1 or a divided dose on days 1 and 8 in combination with Vd at standard doses. Among 18 patients who received belamaf 2.5 mg/kg as a single dose in combination with Vd, ORR was 78% and VGPR rate was 50%. In total, 100% of patients had AEs requiring dose delays, and 72% of patients required dose reductions due to keratopathy and/or thrombocytopenia. Further results are awaited as they mature from this study.

Description, etiology, and management of belamaf-associated ocular adverse events

As detailed above, ocular toxicity has been observed with the use of belamaf and other agents that incorporate MMAF. The precise mechanism of corneal damage has not been fully elucidated, but result in microcystic epithelial damage (microcyst-like epithelial changes or MECs) likely due to non-specific ADC uptake into the actively dividing epithelial cells in the basal layer of the cornea.[17,20–22] Both on-target and off-target corneal toxicities have been described with ADCs, although given that BCMA is not expressed in the cornea, MECs from belamaf are likely due to off-target effects of belamaf.

In the DREAMM-2 study, ophthalmological exams were performed prior to each belamaf dose every 3 weeks which included a (1) slit lamp exam (SLE) for the evaluation of corneal changes and (2) best corrected visual acuity (BCVA) assessment to evaluate changes in vision from baseline. These two findings were graded separately (grades 1–4) using the keratopathy–visual acuity (KVA) scale, which was developed specifically for the DREAMM-2 study. Grading based on the KVA scale served as the basis for dose delays and dose modifications per protocol. In the 2.5 mg/kg cohort, 72% of patients were found to have MECs, 54% of patients had any BCVA changes, and 72% developed both MECs and changes in BCVA, with a maximum severity of grade 3 for both MECs and BCVA in the majority of these patients as per the KVA scale. In contrast, only 25% of patients reported blurred vision and 15% of patients reported dry eyes of any grade as per the CTCAE v4.03 scale, among which the majority were grade 1 in severity. This highlights that ocular exam findings of MECs or changes in BCVA are often not associated with patient-reported ocular symptoms.[17,21]

The median time to the onset and duration of ocular AEs at the 2.5 mg/kg dose were as follows: 37 days and 87 days for MECs, 64 days and 33 days for BCVA changes, 52 days and 43 days for blurred vision, and 42 days and 39 days for dry eyes. At the time of last follow-up at the time of data cut-off, recovery was noted in 48% patients for MECs, 59% for BCVAs, 63% for blurred vision, and 79% for dry eyes.[17,21]

Farooq *et al.* reviewed the corneal findings in the DREAMM-2 study and hypothesized that following systemic administration of belamaf, it enters the cornea *via* tears and/or *via* the vasculature of the limbus. This then leads to internalization of belamaf by the basal corneal epithelium through macropinocytosis. The corneal epithelial cells undergoing apoptosis initially appear in the periphery as MECs under SLE and then subsequently migrate centrally and anteriorly toward the visual axis, leading to visual symptoms. Additional studies are ongoing to confirm this hypothesis and further elucidate the mechanistic details of belamaf-associated keratopathy. Interestingly, macropinocytosis is also thought to

be the etiology responsible for belamaf-induced thrombocytopenia through apoptosis of megakaryocyte progenitors.[20,21]

Agents that inhibit macropinocytosis, such as imipramine, phenoxybenzamine, and vinblastine may be an option to mitigate these effects, but these agents have yet to be tested for this indication in clinical trials.[23] Prophylactic corticosteroid eye drops were found to be of limited benefit in trials of other ADCs, but as noted in the DREAMM-2 ocular substudy, this strategy was deemed to be of no benefit in preventing belamaf-associated keratopathy. Cooling eye masks or vasoconstrictors administered at the start of the infusion have also been used to minimize ocular exposure to belamaf, but the true benefit of these interventions is unclear at this time. At the current time, the main mitigation strategies of belamaf-related corneal toxicity are dose delays and dose reductions to allow time for replacement of corneal epithelial cells.[21] Studies evaluating alternative belamaf dosing strategies including split dosing or less frequent dosing are ongoing or planned in hopes of further mitigating ocular toxicity risks.

Importantly, a recent post-hoc analysis evaluating the impact of prolonged dose delays on response demonstrated that responses were maintained in the majority of these patients. Among 16 of 31 patients who achieved at least a partial response in cohort 1 and had >63 day (three cycle) delay in therapy, 12 (75%) maintained or had deepening of their responses.[24] Since the primary mitigation strategy of ocular toxicity with belamaf are dose delays and dose reductions, these data highlight the feasibility of this approach in patients who are responding to therapy.

Because of the ocular toxicity risk of belamaf, the drug can only be prescribed through a Risk Evaluation and Mitigation Strategy program that patients, healthcare providers, and healthcare facilities must enroll in. It is important to educate patients to self-administer prophylactic preservative-free lubricating eye drops at least four times daily to mitigate dry eye symptoms that are common with belamaf. Belamaf should be avoided in patients with pre-existing corneal epithelial disease, and contact lenses should not be worn unless recommended by an ophthalmologist. Given the unique and frequent corneal ocular AEs reported with belamaf, a multidisciplinary team of oncologists and eye care specialists (general ophthalmologists, optometrists, and/or corneal specialists) is needed to safely treat patients with belamaf. However, with mitigation strategies such as dose delays and dose reductions based on ocular exam findings using the KVA scale and ocular symptoms, belamaf-associated ocular AEs are manageable and reversible with time off therapy.

Current application and future directions of belamaf in RRMM

With the multitude of new agents approved for RRMM in recent years, the question is where does belamaf fit into the current RRMM treatment landscape?

Late RRMM

In its current approved indication, the clear utility for belamaf in the RRMM treatment landscape is in triple-class refractory MM patients. While the ORR of 31% in the 2.5 mg/kg cohort in the DREAMM-2 study is comparable to other recent single-agent myeloma drug approvals,[25–27] the depth (⩾VGPR 19%) and durability of responses (median 11 months) were particularly encouraging. Historically, cytotoxic hyperfractionated cyclophosphamide-based chemotherapy options such as DT-PACE,[28] DCEP,[29] or modified-CBAD[30] have often been used in this setting with significant treatment-related toxicities and short durations of responses. Selinexor is also an option for these patients, which is approved for RRMM patients who have received at least four prior therapies and whose disease is refractory to at least two PIs, two IMiDs, and an anti-CD38 monoclonal antibody based on an ORR of 25%, median PFS of 4.7 months, and median duration of response of 4.4 months in its pivotal registration study targeting triple-class refractory MM patients.[27]

However, with the anticipated approvals in the near future of other BCMA-targeted therapies including BCMA CAR-Ts and TCEs, the use and sequencing of these BCMA-directed therapies in a crowded landscape will become more complex. Early data from BCMA CAR-Ts and TCEs in clinical trials have demonstrated impressive response rates, depth of response and, in

some cases, duration of response.[31–34] Their use may be favored in younger and fit patients given the risks for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) when administering these agents, whereas belamaf may be favored in older, frail patients. An advantage of belamaf is that it is an "off-the-shelf" drug that can be administered immediately in an outpatient setting, which may be particularly important for patients with rapidly progressing disease who cannot wait for apheresis, manufacture, and administration of an autologous CAR-T product. While TCEs are also "off-the-shelf," their use in clinical trials thus far typically requires inpatient hospitalization for CRS/ICANS monitoring for the first several doses before transitioning to outpatient administration, which may be particularly relevant when treatment choices are considered in the community oncology setting. Finally, factors in MM disease biology and the host immune system such as T-cell fitness that could impact responses and inform the optimal sequencing of BCMA-targeted agents will be important research questions as these drugs gain regulatory approval.

Studies evaluating belamaf in combination with novel drugs to augment response in the late RRMM patient population are also ongoing or planned (Table 1). The DREAMM-4 study (NCT03848845) is evaluating the combination of belamaf with the anti-PD-1 monoclonal antibody pembrolizumab. The DREAMM-5 study (NCT04126200) is a platform study evaluating belamaf in combination with other novel agents including GSK3174998 (anti-OX-40 monoclonal antibody), GSK3359609 (anti-ICOS agonist), nirogacestat (small molecule gamma secretase inhibitor), and dostarlimab (anti-PD-1 monoclonal antibody). The combination study with nirogacestat is particularly relevant to BCMA-targeted therapies as gamma secretase inhibitors increase BCMA antigen density on MM cells and decrease soluble BCMA levels in the blood which may act as an "antigen sink" for BCMA-targeted drugs after administration.[35] Finally, the safety and efficacy of belamaf is also being evaluated in special MM patient populations, including those with hepatic impairment in the DREAMM-13 study (NCT04398680) and renal impairment in the DREAMM-12 study (NCT04398745). Notably, in a post-hoc analysis of the DREAMM-2 study, patients with moderate renal impairment (glomerular filtration rate 30–60 mL/min) had similar efficacy and safety data compared with the overall study population.[36] However, belamaf has not been evaluated yet in patients with severe renal impairment (glomerular filtration rate $<$30 mL/min) or patients on hemodialysis, which is the intent of the DREAMM-12 study.

Early RRMM

The role of belamaf is also being investigated in combination studies in early RRMM in several ongoing or planned studies. As discussed earlier, preliminary results of the DREAMM-6 trial (NCT03544281) have been reported demonstrating the safety and early efficacy of belamaf in combination with Vd in RRMM patients with at least one line of prior therapy.[19] The DREAMM-6 study is also evaluating belamaf in combination with Rd in a separate arm with no reported results to date. Additionally, the DREAMM-3 trial (NCT04162210) is a randomized phase III trial comparing single-agent belamaf versus pomalidomide and low-dose dexamethasone (pom/dex) in patients with at least two lines of prior therapy and previous exposure to a PI and lenalidomide. The DREAMM-7 trial (NCT04246047) is randomized phase III trial comparing belamaf plus Vd against daratumumab plus Vd in RRMM with a least one line of prior therapy. Finally, the DREAMM-8 study (NCT04484623) is a randomized phase III study comparing belamaf plus pom/dex versus bortezomib plus pom/dex (PVd) in RRMM patients with at least one line of prior therapy and prior lenalidomide exposure.

These studies will provide important data on the safety and efficacy of belamaf in combination with other approved MM drugs. With the plethora of treatment options in early RRMM, the randomized studies comparing belamaf or belamaf-combinations *versus* standard-of-care combinations such as dara-Vd, PVd, and pom/dex will be critical to further define the role of belamaf in this setting. The ocular AEs and the mandated close ophthalmology monitoring may lead oncologists and patients to consider alternative options other than belamaf in this setting when choosing a regimen in early RRMM, unless superior efficacy is demonstrated in these phase III trials. However, the use of belamaf may also be bolstered if additional mitigation strategies of ocular toxicity are successfully developed, including alternative dosing schedules

Table 1. Ongoing or planned studies with belantamab mafodotin (belamaf).

Study	Phase	Treatment	Patient population	Results
DREAMM-1 (NCT02064387)[14,15]	I	Single-agent belamaf Dose escalation Dose expansion at RP2D (3.4 mg/kg Q3W)	RRMM with ⩾2 lines of therapy including PI, IMiD, and alkylator agent	3.4 mg/kg dose (n = 35) ORR 60% DOR: 14.3 mo PFS: 12 mo ORR: 38.5% in triple-class refractory patients (n = 13)
DREAMM-2 (NCT03525678)[17]	II	Belamaf 2.5 mg/kg Q3W Belamaf 3.4 mg/kg Q3W	RRMM with ⩾3 lines of therapy and refractory to PI and IMiD, and refractory to and/or intolerant to anti-CD38 mAb	2.5 mg/kg (n = 97) ORR: 31% PFS: 2.9 mo DOR: 11 mo OS: 13.7 mo 3.4 mg/kg (n = 99) ORR: 34% PFS: 3.9 mo DOR: 6.2 mo OS: 13.8 mo
DREAMM-3 (NCT04162210)	III	Belamaf *versus* Pomalidomide and dexamethasone	RRMM with ⩾2 lines of therapy including PI and lenalidomide	pending
DREAMM-4 (NCT03848845)	I/II	Belamaf + Pembrolizumab	RRMM with ⩾3 lines of therapy including PI, IMiD, and anti-CD38 mAb	pending
DREAMM-5 (NCT04126200)	I/II	Belamaf in combination with: Substudy 1: GSK3174998 (anti-OX-40 monoclonal antibody) Substudy 2: GSK3359609 (anti-ICOS agonist) Substudy 3: nirogacestat (small molecule gamma secretase inhibitor) Substudy 4: dostarlimab (anti-PD-1 monoclonal antibody)	RRMM with ⩾3 lines of therapy including PI, IMiD, and anti-CD38 mAb	pending
DREAMM-6 (NCT03544281)[19]	I/II	Belamaf (Q3W or split D1 and D8 dose Q3W) in combination with: Arm A: Lenalidomide and dexamethasone Arm B: Bortezomib and dexamethasone	RRMM ⩾1 line of therapy	Arm A: pending Arm B: ORR 78% and ⩾VGPR 50% (preliminary)

(Continued)

Table 1. (Continued)

Study	Phase	Treatment	Patient population	Results
DREAMM-7 (NCT04246047)	III	Belamaf + bortezomib, dexamethasone *versus* Daratumumab + bortezomib, dexamethasone	RRMM ⩾1 line of therapy	pending
DREAMM-8 (NCT04484623)	III	Belamaf + pomalidomide and dexamethasone *versus* Bortezomib + pomalidomide and dexamethasone	RRMM ⩾1 line of therapy including lenalidomide	pending
DREAMM-9 (NCT04091126)	I	Belamaf (multiple dose cohorts) -1.9 mg/kg Q3/4W -1.4 mg/kg Q6/8W -1.9 mg/kg Q6/8W -1.0 mg/kg Q3/4W -1.4 mg/kg Q3/4W -1.9 or 2.5 mg/kg Q9/12W -1.9/2.5 mg/kg Q6/8W (split) -2.5 mg/kg Q6/8W in combination with: bortezomib, lenalidomide, dexamethasone × 8 cycles followed by lenalidomide and dexamethasone	Transplant ineligible NDMM	pending
DREAMM-12 (NCT04398745)	I	Belamaf	Renal Impairment RRMM with ⩾2 lines of therapy including PI and IMiD	pending
DREAMM-13 (NCT04398680)	I	Belamaf	Hepatic Impairment RRMM with ⩾2 lines of therapy including PI and IMiD	pending
ALGONQUIN (NCT03715478)	I/II	Belamaf (Q4W or split D1 and D8 dose Q4W) in combination with: pomalidomide and dexamethasone	RRMM with ⩾2 lines of therapy including PI and lenalidomide	pending

D, day; DOR, duration of response; IMiD, immunomodulatory drug; mAb, monoclonal antibody; mo, month; *n*, number; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; Q, every; RP2D, recommended phase II dose; RRMM, relapsed and/or refractory multiple myeloma; W, week.

and improved supportive care, as the mechanistic details of belamaf-associated keratopathy become better elucidated.

Conclusion

The regulatory approval of belamaf represents a significant advance as the first-in-class ADC and first BCMA-targeted drug approved for the treatment of RRMM based on data from the pivotal DREAMM-2 study. The median duration of response of 11 months in triple-class refractory MM patients is particularly encouraging, and its "off-the-shelf" availability and outpatient administration may confer it advantages over other BCMA-targeting agents that are in development. However, belamaf is frequently associated with ocular AEs, which represents a unique toxicity in MM therapeutics and is managed effectively by dose delays and dose reductions based on ocular exam findings and symptoms. As a result, it is critical that oncologists work closely with eye care specialists as part of a multidisciplinary team when treating patients with belamaf. Results of ongoing combination studies with other novel agents in late RRMM and randomized studies in comparison to standard-of-care approaches in early RRMM are awaited to further define the role belamaf in the RRMM therapeutic landscape.

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