Belantamab mafodotin, lenalidomide and dexamethasone in transplant-ineligible patients with newly diagnosed multiple myeloma: part 1 results of a phase I/II study

Evangelos Terpos,[1] Maria Gavriatopoulou,[1] Ioannis Ntanasis-Stathopoulos,[1] Panagiotis Malandrakis,[1] Despina Fotiou,[1] Magdalini Migkou,[1] Foteini Theodorakakou,[1] Vasiliki Spiliopoulou,[1] Ioannis V. Kostopoulos,[2] Rodanthi-Eleni Syrigou,[1] Evangelos Eleutherakis-Papaiakovou,[1] Stavros Gkolfinopoulos,[3] Ourania E. Tsitsilonis,[2] Efstathios Kastritis[1] and Meletios A. Dimopoulos[1]

[1]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; [2]Department of Biology, School of Science, National and Kapodistrian University of Athens, Athens, Greece and [3]Health Data Specialists, Dublin, Ireland

Correspondence: E. Terpos
eterpos@med.uoa.gr

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Abstract

Preclinical and clinical data demonstrate synergy between belantamab mafodotin (belamaf) and immunomodulatory drugs with limited overlapping toxicities. We investigated the safety and efficacy of belamaf with lenalidomide 25 mg on days 1-21 every 28 days and dexamethasone 40 mg weekly (belamaf-Rd) in transplant-ineligible patients with newly diagnosed multiple myeloma. Thirty-six patients (median age, 72.5 years) were randomized to receive belamaf at three different doses (2.5, 1.9, or 1.4 mg/kg) every 8 weeks. The dosing schedule was extended to every 12 weeks to mitigate ocular toxicity. Most common grade ≥3 adverse events were fatigue (n=21, 58.3%), rash (n=6, 16.7%), diarrhea (n=8, 22.2%) and COVID-19 (n=5, 13.9%). Grade 3-4 ocular adverse events, comprising visual acuity decline from baseline and/or keratopathy, were reported in 39/216 (18.1%), 33/244 (13.5%), and 26/207 (12.6%) ophthalmological assessments in the 2.5, 1.9, and 1.4 mg/kg cohorts, respectively. Importantly, grade 3-4 keratopathy was identified in 9/216 (4.2%), 1/244 (0.4%) and 1/207(0.5%) assessments. Most patients (32/36, 88.9%) were treated with the extended, every-12-week schedule, during which 40, 33 and 16 doses were withheld due to ocular adverse events in the 2.5, 1.9, and 1.4 mg/kg cohorts, respectively. Overall, the rates of very good partial response and better and complete response and better were 83.3% and 52.8%, respectively, without significant differences among cohorts. Over a median follow-up of 20.3 months no disease progression was reported; six patients discontinued treatment due to infection-related death (4 cases of COVID-19, 2 cases of pneumonia) and one patient withdrew consent. Based on the toxicity/efficacy balance, the recommended phase II dose was 1.9 mg/kg every 8 weeks, extended to every 12 weeks because of toxicity. In conclusion, Belamaf-Rd, with the extended schedule for belamaf, showed important clinical activity and a significant improvement of ocular adverse events with minimal impact on vision-related functioning in an elderly, non-transplant eligible population.

Introduction

The current gold standard for the treatment of patients with newly diagnosed multiple myeloma (NDMM) who are not eligible for autologous stem cell transplantation (ASCT) involves combination therapy with lenalidomide and dexamethasone (Rd), supplemented by a third antimyeloma agent that has a different mechanism of action, such as a proteasome inhibitor (bortezomib - VRd) or an anti-CD38 monoclonal antibody (daratumumab - DaraRd). The quadruplet of daratumumab with melphalan, bortezomib and prednisone (DaraVMP) is an equal option for the upfront treatment of transplant-ineligible NDMM.[1]

The reported median progression-free survival (PFS) for patients treated with VRd was 41 months and the median overall survival (OS) was not reached in the SWOG S0777 study.[2] However, a clear survival benefit with VRd over Rd was not evident in the subgroup of elderly patients aged 65 years or older.[2] In the ALCYONE trial, the median PFS for patients treated with DaraVMP was 36.4 months, and the median OS was 82.7 months at a median follow-up of 74.7 months.[3] Similarly, at a median follow-up of 64.5 months, median PFS and OS were not reached for patients treated with DaraRd in the MAIA study.[4] DaraVMP and DaraRd produced better outcomes for patients than VMP and Rd, respectively, regardless of frailty status; however, frail

patients had inferior survival outcomes compared with non-frail patients in both the ALCYONE and MAIA studies.[5,6] Therefore, new treatment approaches need to be explored to further optimize outcomes, especially for frail patients who have high-risk disease and, by extension, poor prognosis,[7] considering also the debatable cost-effectiveness of adding anti-CD38 monoclonal antibodies to first-line treatment.[8,9]

B-cell maturation antigen (BCMA) is a cell membrane receptor expressed on late-stage B cells and plasma cells.[10] The pivotal DREAMM-1 and DREAMM-2 clinical trials evaluated the efficacy and tolerability of anti-BCMA targeting and established BCMA-directed therapy as the fourth pillar of myeloma treatment, along with proteasome inhibitors, immunomodulatory drugs and anti-CD38 antibodies.[11,12] Currently, the three main anti-BCMA therapeutic categories are antibody-drug conjugates, bispecific antibody constructs, and chimeric antigen receptor-modified T-cell therapy.[13] Ongoing trials are evaluating each of these treatment strategies in the first-line setting.[14-16]

Belantamab mafodotin (belamaf; GSK2857916) is a first-in-class antibody-drug conjugate, which comprises a humanized IgG1κ monoclonal antibody and the cytotoxic agent monomethyl auristatin F.[17] Belamaf has demonstrated important efficacy in heavily pre-treated patients with relapsed/refractory MM (RRMM) who had received four or more prior lines of treatment.[11,12] In the DREAMM-2 study, belamaf monotherapy was administered at a dose of 2.5 mg/kg every 3 weeks (q3w) and resulted in an overall response rate (ORR) of 32% with a median PFS and OS of 2.8 and 13.7 months, respectively.[18] Real-world studies of belamaf monotherapy provided similar results with a marked survival benefit among responders.[19-22] Moreover, although belamaf monotherapy was not statistically superior to pomalidomide with dexamethasone in terms of PFS prolongation (11.2 *vs.* 7 months, respectively, *P*=0.56) in the DREAMM-3 study including RRMM patients who had received at least two prior lines of therapy, the responses were deeper and more durable with belamaf.[23]

In terms of safety, a common belamaf-related adverse event is ocular toxicity, which is usually reversible but may require long-term use of supportive eye medications. However, although cross-trial comparisons should be made with caution, it seems that belamaf is associated with a lower infection risk overall compared with that of anti-myeloma immunotherapies such as bispecific antibodies.[13]

The efficacy of belamaf increases substantially when it is given in combination with other anti-myeloma agents, as in such cases a synergistic effect may take place. For example, the combination of belamaf, pomalidomide and dexamethasone produced a median PFS of 15.6 months and an ORR of 86% in triple-class-exposed patients, with 60% of the patients achieving a very good partial response (VGPR) or better.[24] Similarly, the combination of belamaf, carfilzomib and dexamethasone produced a VGPR or better in 60% of relapsed patients who had received one or more lines of therapy.[25] Finally, lenalidomide potentiates the antibody-dependent cell-mediated cytotoxicity and apoptotic effect of belamaf on myeloma cells *in vitro*.[10]

Taking the above into consideration, we investigated the safety profile and potential benefit of the triplet combination of belamaf, lenalidomide and dexamethasone (belamaf-Rd) in patients with NDMM not eligible for ASCT in the phase I/II clinical trial BelaRd (ClinicalTrials.gov number: NCT04808037), an ongoing, open-label, single-center trial conducted by the Hellenic Society of Hematology (trial number: EAE-2020/MM0107) in Greece; the trial aims to enroll a total of 66 transplant-ineligible NDMM patients.

The main objective of part 1 of the BelaRd study was to establish the recommended phase II dose (RP2D) of belamaf in combination with standard dose Rd in transplant-ineligible patients with NDMM. The safety and efficacy of the RP2D will be determined in part 2 of the study. For part 1, study outcomes included the safety and tolerability of belamaf-Rd as determined by the number of participants with dose-limiting toxicities (DLT), the number of participants with adverse events (AE) and serious AE, along with an evaluation of preliminary clinical activity, in each of the three dosing cohorts.

Methods

Patients

Key eligibility criteria for enrollment of patients in the study are shown in *Online Supplementary Table S1*. The study was approved by the institutional review board. All patients provided written informed consent before entering the study, which was performed in accordance with the Declaration of Helsinki and its amendments.

The study is divided into two parts. Part 1 focused on assessing the safety and tolerability of three different doses of belamaf (cohort 1: 2.5 mg/kg, cohort 2: 1.9 mg/kg, cohort 3: 1.4 mg/kg) in combination with Rd in a group of 36 patients to determine the RP2D. Patients were randomly allocated to each of the three cohorts (1:1:1). Initially, 18 patients were randomized (6 in each cohort) and a safety review was performed at the end of the DLT period of 4 weeks from the first dose of the last enrolled patient. The safety assessment was in favor of study continuation and another 18 patients were randomized (another 6 in each cohort). Another safety review was performed after the completion of the DLT period for all 36 patients to reach consensus regarding the RP2D. Patients receive treatment until documented disease progression, consent withdrawal, death or unacceptable toxicity.

Initially, belamaf is administered intravenously every 8 weeks (q8w), while dosing is adjusted every 12 weeks (q12w) depending on toxicity. More specifically, if at least one grade ≥2 ocular adverse event (OAE) is observed, belamaf

dosing is withheld, and restarted when all OAE are grade ≤1. From that point forward, all subsequent belamaf doses are rescheduled to q12w. OAE are defined as a Snellen best corrected visual acuity (BCVA) decline from baseline and/or corneal findings suggestive of keratopathy.

Lenalidomide is administered at a dose of 25 mg *po* for 21 days in each 28-day cycle of treatment and dexamethasone is administered weekly at a dose of 40 mg *po*, according to the approved Rd regimen. Patients aged 75 years or older started dexamethasone at a dose of 20 mg weekly, whereas patients with renal impairment at baseline started with a reduced lenalidomide dose. The dose levels of lenalidomide and dexamethasone were adjusted according to the highest grade of hematologic and non-hematologic toxicity attributed to each drug (*Online Supplementary Material*). Lenalidomide dose levels included 25 mg, 20 mg, 15 mg, 10 mg, and 5 mg, whereas dexamethasone dose levels included 40 mg, 20 mg, 12 mg, 8 mg, and 4 mg.

All NDMM patients enrolled in the study received appropriate antiviral, antibiotic and antithrombotic prophylaxis as per standard clinical practice. Infection prevention included oral valacyclovir 500 mg daily for varicella zoster virus, oral trimethoprim/sulfamethoxazole 800/160 mg three times weekly for *Pneumocystis carinii* and oral levofloxacin 500 mg daily during the first 3 months of treatment. Additionally, patients were instructed to get vaccinated against coronavirus disease 2019 (COVID-19), *Streptococcus pneumoniae* and influenza.

Study outcomes and assessments

DLT were evaluated during the first cycle of treatment and included the AE shown in *Online Supplementary Table S2*. During part 1, ocular safety was monitored closely through several assessments, including an ophthalmological examination performed at baseline, every 4 weeks (before the initiation of each cycle of treatment) and as clinically indicated. Ocular symptoms and BCVA were assessed and a slit lamp corneal examination was performed. Evaluation of the lens, fundoscopy and intraocular pressure measurements were performed as required. In addition, the Ocular Surface Disease Index was used to measure dry eye disease and its impact on activities of daily living. OAE

Table 1. Patients' demographics and baseline disease characteristics.

	Cohort 1 2.5 mg/kg q8w N=12	Cohort 2 1.9 mg/kg q8w N=12	Cohort 3 1.4 mg/kg q8w N=12
Age in years, median (range)	75.0 (66.0-86.0)	74.5 (68.0-82.0)	69.0 (64.0-79.0)
Gender, N (%) Male Female	 8 (66.7) 4 (33.3)	 5 (41.7) 7 (58.3)	 6 (50.0) 6 (50.0)
ECOG PS, N (%) 0 1 2	 4 (33.3) 6 (50.0) 2 (16.7)	 3 (25.0) 9 (75.0) 0 (0.0)	 8 (66.7) 4 (33.3) 0 (0.0)
ISS, N (%) I II III	 4 (33.3) 5 (41.7) 3 (25.0)	 3 (25.0) 7 (58.3) 2 (16.7)	 4 (33.3) 7 (58.3) 1 (8.3)
R-ISS, N (%) I II III	 1 (8.3) 9 (75.0) 2 (16.7)	 2 (16.7) 10 (83.3) 0 (0.0)	 3 (25.0) 8 (66.7) 1 (8.3)
Lytic bone lesions, N (%)	7 (58.3)	7 (58.3)	5 (41.7)
Extramedullary disease, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
High-risk cytogenetics,[a] N (%) 17p13 t (4;14) t (14;16)	1 (8.3) 0 (0.0) 0 (0.0) 1 (8.3)	2 (16.7) 0 (0.0) 2 (16.7) 0 (0.0)	0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0)
IMWG Frailty Score, N (%) Fit (score=0) Intermediate fitness (score=1) Frail (score ≥ 2)	 0 (0.0) 10 (83.3) 2 (16.7)	 0 (0.0) 11 (91.7) 1 (8.3)	 0 (0.0) 11 (91.7) 1 (8.3)

[a]High-risk cytogenetics defined as del 17p13, t(14:16) or t(4:14). q8w: every 8 weeks; ECOG PS: Eastern Cooperative Oncology Performance Status; ISS: International Staging System; R-ISS: Revised International Staging System; IMWG: International Myeloma Working Group.

were graded on the Keratopathy Visual Acuity scale, while ocular symptoms and all non-ocular AE were classified according to the Common Terminology Criteria for Adverse Events version 5.0.

Efficacy assessments were performed on day 1 of each 28-day cycle. The ORR was defined as the percentage of participants with a confirmed partial response (PR), VGPR or (stringent) complete response (CR) according to the International Myeloma Working Group response criteria.[26-28] Further information on methodology is provided in the *Online Supplementary Material*.

Results

Patients and treatment characteristics

Overall, 36 patients were included in part 1 of the BelaRd study and were equally allocated to the three dosing cohorts (12 patients each). The median age of the whole cohort was 72.5 years (range, 64-86 years); 19 patients (52.8%) were males. Eastern Cooperative Oncology Group performance status at baseline was 0 in 15 (41.7%) patients, 1 in 19 (52.8%) patients, and 2 in two (5.6%) patients. According to the International Myeloma Working Group frailty score, 32 (88.9%) patients were characterized as intermediate-fit and four (11.1%) patients as frail. The patients' disposition according to prognostic staging systems was 11 (30.6%), 19 (52.8%), and six (16.7%) for International Staging System (ISS) 1, 2 and 3, respectively, and six (16.7%), 27 (75.0%), and three (8.3%) for the Revised ISS 1, 2 and 3, respectively. Twenty-seven (75.0%) patients had IgG myeloma, seven (19.4%) had IgA myeloma and two (5.6%) patients had light chain myeloma. The patients' demographics and baseline characteristics are provided in Table 1.

The median follow-up time for the whole study cohort at the time of this analysis was 20.3 months (range, 3.2-26.8 months). Overall, 31 patients (86.1%) had one or more doses of belamaf withheld due to AE. The proportions of patients with one or more dose withheld in the 2.5, 1.9, and 1.4 mg/kg groups were eight (66.7%), 11 (91.7%), and 12 (100%). All dose suspensions were due to OAE. At the cut-off date, 29 (80.6%) patients were still on treatment, while seven (19.4%) had discontinued: six due to infection-related death

Table 2. Ocular adverse events and time to resolution.

	Cohort 1 2.5 mg/kg q8w N=216	Cohort 2 1.9 mg/kg q8w N=244	Cohort 3 1.4 mg/kg q8w N=207
Total N of OAE[a] /Total N of ocular assessments (%) Grade 0-1 Grade 2 Grade 3-4	 86 (39.3) 91 (43.9) 39 (18.1)	 130 (55.7) 81 (31.1) 33 (13.5)	 115 (56.5) 66 (31.4) 26 (12.6)
Total N of BCVA decline assessments/Total N of ocular assessments (%) Grade 0-1 Grade 2 Grade 3-4[b]	 90 (41.7) 93 (43) 33 (15.3)	 139 (57) 73 (30) 32 (13)	 119 (57.5) 63 (30.4) 25 (12.1)
Total N of keratopathy assessments/Total N of ocular assessments (%) Grade 0-1 Grade 2 Grade 3-4	 179 (82.9) 28 (13.0) 9 (4.2)	 214 (87.3) 30 (12.2) 1 (0.4)	 185 (89.4) 21 (10.1) 1 (0.5)
N of assessments with meaningful BCVA decline[c] with at least 3 lines drop in the better seeing eye/Total N of ocular assessments (%)	21/216 (9.7)	24/244 (9.8)	17/201 (8.5)
Time to resolution of BCVA decline in months, median (range)	2.1 (0.3-6.3)	1.9 (0.9-6.2)	1.9 (0.9-8.6)
Time to resolution[d] of meaningful BCVA decline with at least 3 lines drop in better seeing eye in months, median (range)	1.2 (1.0-4.5)	1.4 (0.8-2.0)	1.55 (0.9-5.5)
Time to resolution[d] of OAE in months, median (range)	2.1 (0.3-6.3)	1.9 (0.9-6.2)	1.9 (0.9-8.6)
Time to resolution[d] of BCVA decline in months, median (range)	2.1 (0.3-6.3)	1.9 (0.9-6.2)	1.9 (0.9-8.6)
Time to resolutiond of keratopathy in months, median (range)	1.0 (0.5-7.4)	1.4 (0.9-2.8)	1.0 (0.9-3.7)

[a]Ocular adverse events (OAE) in this analysis describe assessments of decreased best corrected visual acuity (BCVA) from baseline (cycle 1, day 1) and assessments of keratopathy. These assessments are graded by the Keratopathy Visual Acuity scale. In a each assessment, the maximum grade of the aforementioned is presented. [b]No grade 4 change in BCVA was observed. [c]Meaningful BCVA decline is defined as BCVA decrease worse than 20/50 at the better-seeing eye. The better-seeing eye was considered the eye that had higher visual acuity at baseline (based on the BCVA). Patients with BCVA worse than 20/50 in both eyes at baseline were excluded from this analysis. [d]For meaningful BCVA decline with at least 3 lines drop in better seeing eye, resolution was considered when the BCVA became 20/50 or better, or the decline was less than 3 lines; while for the resolution of OAE, BCVA decline and keratopathy, resolution was considered when the grade became ≤1. q8w: every 8 weeks; OAE: ocular adverse events; BCVA: best corrected visual acuity.

(COVID-19: 1, 1, and 2; pneumonia: 1, 1, and 0, for the 2.5, 1.9, and 1.4 mg cohorts, respectively) and one withdrew consent due to personal reasons related to inability to visit the hospital according to the study protocol.

Dose intensity (mg/kg/q4w) for each patient was defined as the total belamaf administered in mg/kg divided by the overall number of cycles per patient. For the 2.5, 1.9, and 1.4 mg/kg cohorts, the intended dose intensity was 1.25, 0.95, and 0.70, while the observed median dose intensity was 0.82, 0.65, and 0.50, respectively.

Recommended phase II dose selection

After reviewing all the safety and efficacy data, the safety review committee of the study concluded that the RP2D of belamaf should be 1.9 mg/kg q8w, extended to q12w to account for toxicity. This dose optimally balances the toxicity/efficacy ratio of the belamaf-Rd regimen because, compared to the higher dose of 2.5 mg/kg, equally deep responses and fewer OAE were reported.

Safety

OAE, including a decline in BCVA from baseline and keratopathy, were reported in 191/216 (88.4%), 200/244 (82.0%), and 168/207 (81.2%) ophthalmological assessments in the three cohorts (Table 2), while grade ≥3 OAE were reported in 39/216 (18.1%), 33/244 (13.5%), and 26/207 (12.6%) of the assessments. The median times to the first grade ≥2 OAE were 3.9, 4.5 and 5.9 months for the 2.5, 1.9 and 1.4 mg/kg cohorts, respectively. Among the 216, 244, and 207 ophthalmological assessments performed on patients in the 2.5, 1.9 and 1.4 mg/kg cohorts, a meaningful decline in BCVA (BCVA <20/50) with a drop of at least three lines in the better seeing eye was observed in 21 (9.7%), 24 (9.8%), and 17 (8.5%) assessments, with median times to resolution of 1.2, 1.4, and 1.6 months, respectively. Additionally, BCVA ≤20/200 with a drop of at least three lines

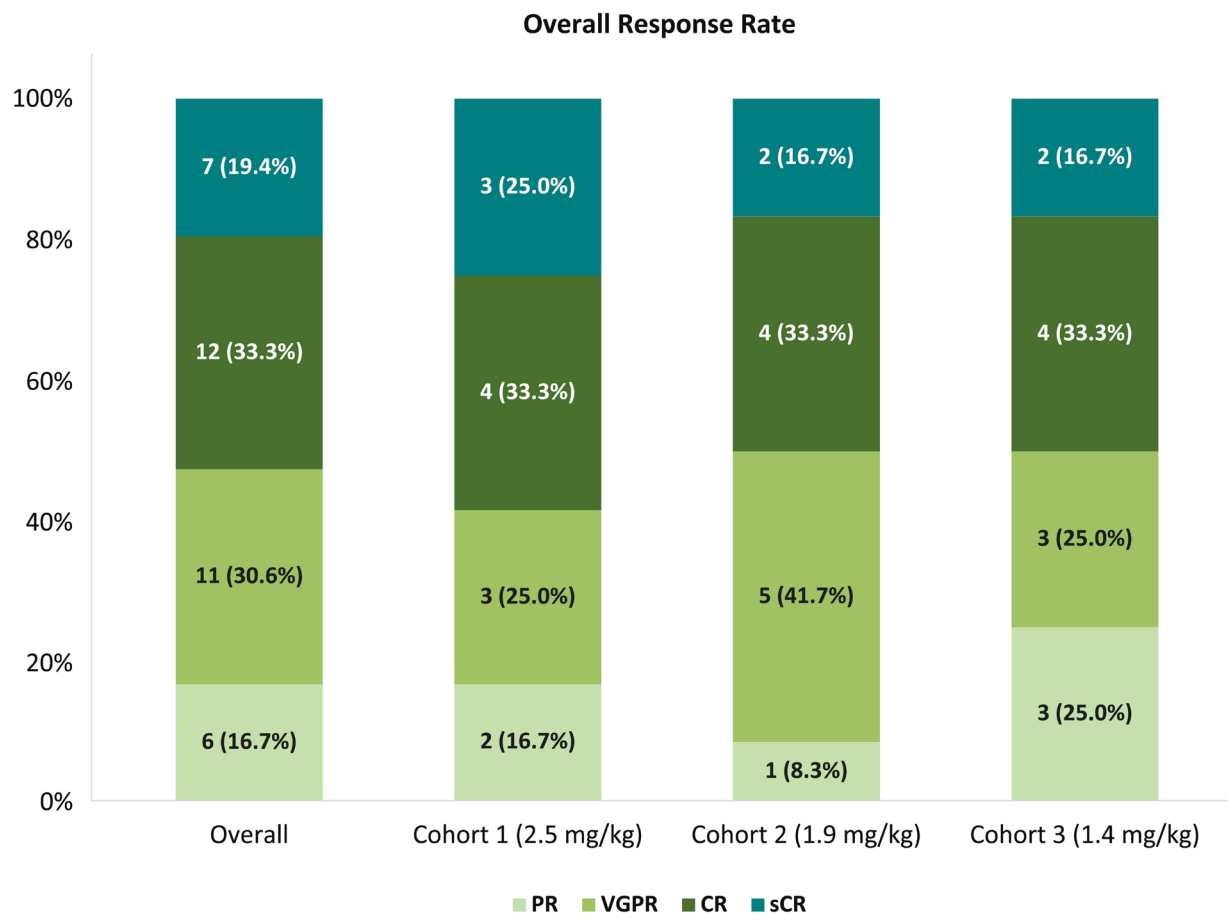
Table 3. Safety overview.

	Cohort 1 2.5 mg/kg q8w N=12		Cohort 2 1.9 mg/kg q8w N=12		Cohort 3 1.4 mg/kg q8w N=12	
MedDRA preferred term	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Dose-limiting toxicities, N (%)						
Fatigue	2 (16.7)	2 (16.7)	3 (25.0)	3 (25.0)	1 (8.3)	1 (8.3)
Rash	0 (0.0)	0 (0.0)	1 (8.3)	1 (8.3)	1 (8.3)	1 (8.3)
Most common[a] treatment-emergent adverse events, N (%)						
Leukopenia	5 (41.7)	2 (16.7)	3 (25.0)	0 (0.0)	3 (25.0)	0 (0.0)
Thrombocytopenia	4 (33.3)	0 (0.0)	2 (16.7)	0 (0.0)	5 (41.7)	0 (0.0)
Cataract	2 (16.7)	1 (8.3)	3 (25.0)	3 (25.0)	4 (33.3)	4 (33.3)
Dry eye	11 (91.7)	3 (25.0)	12 (100.0)	1 (8.3)	12 (100.0)	1 (8.3)
Eye irritation	4 (33.3)	0 (0.0)	3 (25.0)	0 (0.0)	4 (33.3)	0 (0.0)
Foreign body in eye	8 (66.7)	0 (0.0)	7 (58.3)	0 (0.0)	9 (75.0)	0 (0.0)
Keratopathy	11 (91.7)	1 (8.3)	12 (100.0)	1 (8.3)	12 (100.0)	1 (8.3)
Lacrimation increased	4 (33.3)	0 (0.0)	1 (8.3)	0 (0.0)	1 (8.3)	0 (0.0)
Decreased vision[b]	10 (83.3)	7 (58.3)	12 (100.0)	9 (75.0)	12 (100.0)	9 (75.0)
Vitreous floaters	4 (33.3)	0 (0.0)	4 (33.3)	0 (0.0)	4 (33.3)	0 (0.0)
Diarrhea	5 (41.7)	2 (16.7)	6 (50.0)	3 (25.0)	5 (41.7)	3 (25.0)
Fatigue	7 (58.3)	7 (58.3)	8 (66.7)	7 (58.3)	7 (58.3)	7 (58.3)
COVID-19	5 (41.7)	2 (16.7)	5 (41.7)	1 (8.3)	6 (50.0)	2 (16.7)
Rash	2 (16.7)	2 (16.7)	2 (16.7)	2 (16.7)	4 (33.3)	2 (16.7)
Fatal events, grade 5, N (%)						
COVID-19	1 (8.3)		1 (8.3)		2 (16.7)	
Pneumonia	1 (8.3)		1 (8.3)		0 (0.0)	

[a]Frequency of ≥15% in the overall population. [b]Decreased vision is used in the present analysis to describe any event suggesting a deterioration in visual acuity; it corresponds to the following MedDRA terms: vision blurred, visual acuity reduced and visual impairment. The worst grade of the aforementioned terms is presented. q8w: every 8 weeks; MedDRA: Medical Dictionary for Regulatory Activities; COVID-19: coronavirus disease 2019.

in the better-seeing eye was noted in only two (0.9%), three (1.2%), and eight (3.9%) cases. Keratopathy of any grade was evident in 136/216 (63.0%), 130/244 (53.3%) and 94/207 (45.4%) assessments, while grade ≥3 keratopathy was noted in 11/667 (1.6%), nine of which were reported in the 2.5 mg/kg cohort. Across all cohorts, the most frequently reported grade ≥3 ocular symptom was visual impairment (26/665, 3.9%). Regarding the Ocular Surface Disease Index, from 202, 234, and 196 responses received, the numbers of "all/most of the time" worst responses in the ocular symptoms category (gritty eyes, sensitivity to light, painful or sore eyes, blurred vision, poor vision) were six (3.0%), six (2.6%), and eight (4.1%), while the respective proportions in the activities of daily living category (reading, driving at night, working with a computer or bank machine, watching television) were six (3.0%), four (1.7%), and three (1.5%) for the 2.5, 1.9 and 1.4 mg/kg cohorts, respectively. Interpreting these results, it is important to note that while ocular symptoms were frequently reported they had minimal impact on the patients' daily activities. Overall, belamaf administration was withheld (delayed or skipped) in 134 assessments out of 386 planned infusions (34.7%) in both the q8w and q12w schedules due to OAE, while grade ≥2 OAE were reported for all patients who transitioned from the q8w to the q12w schedule. In the extended q12w schedule, doses were withheld in 58.0% (40/69), 40.3% (33/82), and 30.8% (16/52) assessments in the 2.5, 1.9, and 1.4 mg/kg cohorts, respectively. Importantly, the percentage of doses skipped in the 2.5 mg/kg cohort was twice the percentage of doses skipped in the 1.4 mg/kg cohort. Moreover, the median delays for belamaf re-administration following an OAE-related dose suspension were 8.0, 4.4, and 4.6 weeks for the 2.5, 1.9 and 1.4 mg/kg cohorts, respectively, reflecting a substantial difference in terms of ocular safety.

DLT were reported in eight patients (2, 4, and 2 in the



	Overall	Cohort 1	Cohort 2	Cohort 3
Time to first response (months), median (min-max)	1.0 (0.9-3.8)	1.1 (1.0-2.1)	1.0 (0.9-3.8)	1.0 (1.0-2.0)
Time to ≥CR (months), median (min-max)	13.4 (2.8-24.8)	11.5 (4.4-23.1)	13.0 (2.8-18.0)	14.8 (10.4-24.8)
Time to ≥VGPR (months), median (min-max)	11.9 (2.8-24.8)	11.5 (2.9-23.1)	12.2 (2.8-18.0)	13.2 (2.8-24.8)

Figure 1. Overall response rate and time to response. PR: partial response; VGPR: very good partial response; CR: complete response; sCR: stringent complete response; min: minimum; max: maximum.

2.5, 1.9 and 1.4 mg/kg cohorts, respectively), and included grade 3 fatigue (n=6) and grade 3 rash (n=2) (Table 3). No hematologic or ocular DLT emerged. The most common (affecting ≥15% of the patients) non-ocular grade ≥3 treatment-emergent AE, overall and in each dosing cohort, were as follows: fatigue (n=21, 58.3%; 7 [58.3%], 7 [58.3%], and 7 [58.3%]), rash (n=6, 16.7%; 2 [16.7%], 2 [16.7%], and 2 [16.7%]), diarrhea (n=8, 22.2%; 2 [16.7%], 3 [25.0%], and 3 [25.0%]) and COVID-19 (n=5, 13.9%; 2 [16.7%], 1 [8.3%], and 2 [16.7%]) (Table 3). Regarding grade ≥3 infections other than COVID-19, pneumonia was reported for three patients (1 in each cohort, 8.3%) and lower respiratory tract infection for one patient in cohort 3. Serious AE were reported in five (41.7%), two (16.7%) and four (33.3%) patients in the 2.5, 1.9 and 1.4 mg/kg cohorts, respectively. There were six infection-related fatal events; four patients died due to COVID-19 (1, 1, and 2 in the 2.5, 1.9 and 1.4 mg/kg cohorts, respectively) and two patients due to pneumonia (1, 1, and 0 in the 2.5, 1.9 and 1.4 mg/kg cohorts). Furthermore, no grade ≥3 thrombocytopenias or infusion-related reactions were reported.

Hypogammaglobulinemia (IgG <400 mg/dL) was a common finding during the study, manifesting in 27 of 36 (75.0%) patients, while severe hypogammaglobulinemia (IgG <200 mg/dL) occurred in 14 of the 36 (38.9%) patients. In order to decrease the risk of severe infections, it was decided to administer intravenous/subcutaneous immunoglobulin to all ongoing patients.

Efficacy

The ORR was 100% across all cohorts (Figure 1). More specifically, a CR or better was achieved by seven (58.3%), six (50.0%), and six (50.0%) patients, a VGPR or better by ten (83.3%), 11 (91.7%) and nine (75.0%) and a PR by two (16.7%), one (8.3%) and three (25.0%) of the patients in the 2.5, 1.9 and 1.4 mg/kg cohorts. The median (range) times to first response were 1.1 (1.0-2.1), 1 (0.9-3.8), and 1 (1.0-2.0) months, whereas the median (range) times to best response were 10.5 (1.0-23.1), 11.8 (2.8-18.0), and 8.0 (2.8-24.8) months for the respective cohorts. In the subgroup of frail patients (4/36, 11.1%), one achieved a stringent CR, one a VGPR and one had a PR. In the subgroup of patients with two or more cytogenetic abnormalities (4/36, 11.1%), two had a stringent CR and the other two had a VGPR.

After a median follow-up of 20.3 months, no disease progression was observed, the median PFS, median time to progression and median OS were not reached, and responses continue to deepen across all cohorts. The Kaplan-Meier curve for PFS and time to progression is shown in Figure 2, while response evolution during treatment per patient is shown in Figure 3.

Additionally, among 19 patients who manifested a CR or better and were evaluated for minimal residual disease using next-generation flow, 14 (73.7%) were negative at the 1×10^{-5} sensitivity level, accounting for six (85.7%), five (83.3%) and three (50%) patients in the 2.5, 1.9 and 1.4 mg/kg cohorts, respectively.

Discussion

The triplet combination of belamaf-Rd demonstrated tolerability and sustainable efficacy in the treatment of transplant-ineligible NDMM patients, in a less intensified dosing scheme for belamaf compared to the monotherapy dosing schedule of 2.5 mg/kg q3w used in the DREAMM-2 study.[18] Simulations based on DREAMM-1 and DREAMM-2 data have suggested that dose reductions to 1.9 or 1.4 mg/kg, as well as prolongation of dose intervals, may be associated with reduced risk and duration of grade ≥2 OAE, without compromising efficacy.[29] For this reason, studies investigating belamaf combinations are designed with lower dose intensity than that used in DREAMM-2, in order to reduce both ocular and non-ocular additive toxicity.[30-32] In line with this, we planned three distinct cohorts, with belamaf administered at 2.5, 1.9 and 1.4 mg/kg q8w, considering also that our patients are unfit for ASCT due to age and/or comorbidities. In order to further reduce the risk of OAE in this frail population, the dosing interval was extended to q12w at the first sign of a grade ≥2 OAE. With the q12w interval, fewer doses were withheld in the 1.9 and 1.4 mg/kg cohorts than in the 2.5 mg/kg cohort, and the time required to restart belamaf administration was shorter. Additionally, similar responses were observed across all cohorts, although the response rate was seemingly higher in the 2.5 and 1.9 mg/kg cohorts than in the 1.4 mg/kg cohort. Taking this into account and considering the high patient variability in terms of toxicity, we decided to select 1.9 mg/kg as the RP2D.

There are two ongoing studies evaluating belamaf-VRd in

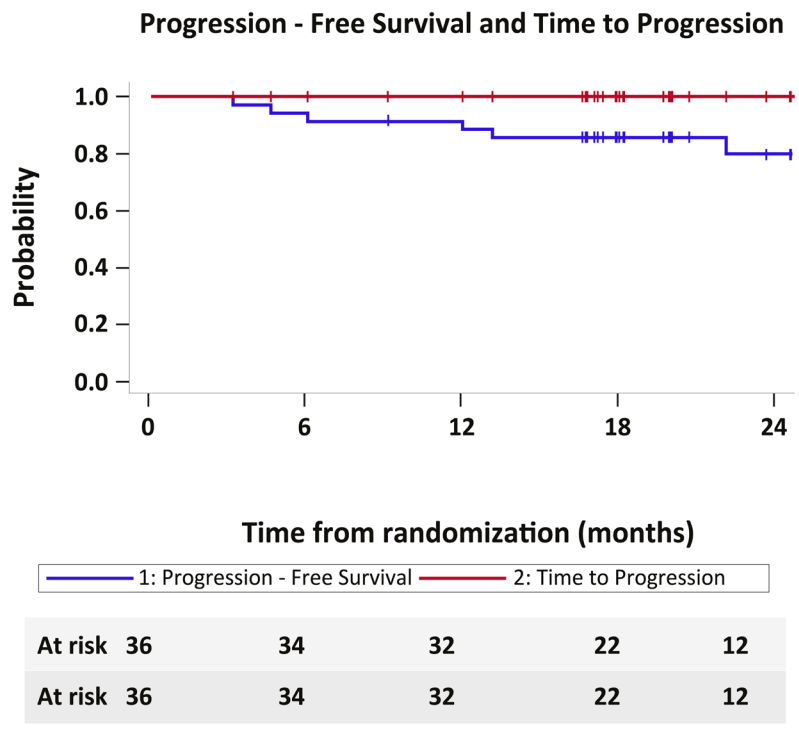


Figure 2. Progression-free survival and time to progression.

NDMM patients. The phase I DREAMM-9 study is evaluating the combination with different belamaf dose levels and dosing frequency in transplant-ineligible NDMM patients.[16] In all cohorts, belamaf is administered at more extended time intervals after eight cycles of treatment. More specifically, the following dosing schemes for belamaf are being evaluated: 1.9 mg/kg every 3 and then every 4 weeks, 1.4 mg/kg every 6 and then every 8 weeks, 1.9 mg/kg every 6 and then every 8 weeks, 1.0 mg/kg every 3 and then every 4 weeks, 1.4 mg/kg every 3 and then every 4 weeks, 1.4 mg/kg for the first dose followed by 1.0 mg/kg every 9 and then every 12 weeks, and 1.9 mg/kg for the first dose followed by 1.4 mg/kg every 9 and then every 12 weeks. An interim analysis showed an ORR of >79% for all cohorts with at least 2 months of median follow-up, whereas the ORR were 100% and 92% in the 1.9 and 1.4 mg/kg cohorts, respectively. A VGPR or better was observed in 92% and 85% and 100% and 91% of patients in the 1.9 and 1.4 mg/kg dose cohorts, at the intervals of 3 and 4 and 6 and 8 weeks, respectively. In our study, a VGPR or better was achieved in 92% and 75% of patients in the 1.9 and 1.4 mg/kg dose cohorts with the extended belamaf schedule. Additionally, in frail patients and patients with two or more cytogenetic abnormalities, a VGPR or better was achieved in 75% and 100% of the patients, respectively. However, due to the very low number of patients in these subgroups, the role of belamaf for high risk and frail patients remains to be determined in part 2 of the study. Although cross-trial comparisons should be approached with caution, it should be noted that responses are comparable between the two studies, even though a proteasome inhibitor is included in the treatment in DREAMM-9.

The GEM-BELA-VRd study evaluated the combination of belamaf at a dose of 2.5 mg/kg every 8 weeks in combination with VRd in transplant-eligible patients with NDMM. The interim analysis on 40 patients who had completed induction with four cycles of belamaf-VRd showed an ORR of 82% (69% VGPR or better).[33] The exact impact of integrating anti-BCMA targeted therapies in the upfront treatment of patients with NDMM remains to be determined in future studies with long follow-up and relevant endpoints such as time to second progression of disease or death (PFS2). Although there are limited data showing a potentially reduced activity of anti-BCMA chimeric antigen receptor T-cell immunotherapy following anti-BCMA treatment, the sequence of the available drug combinations may play a key role.

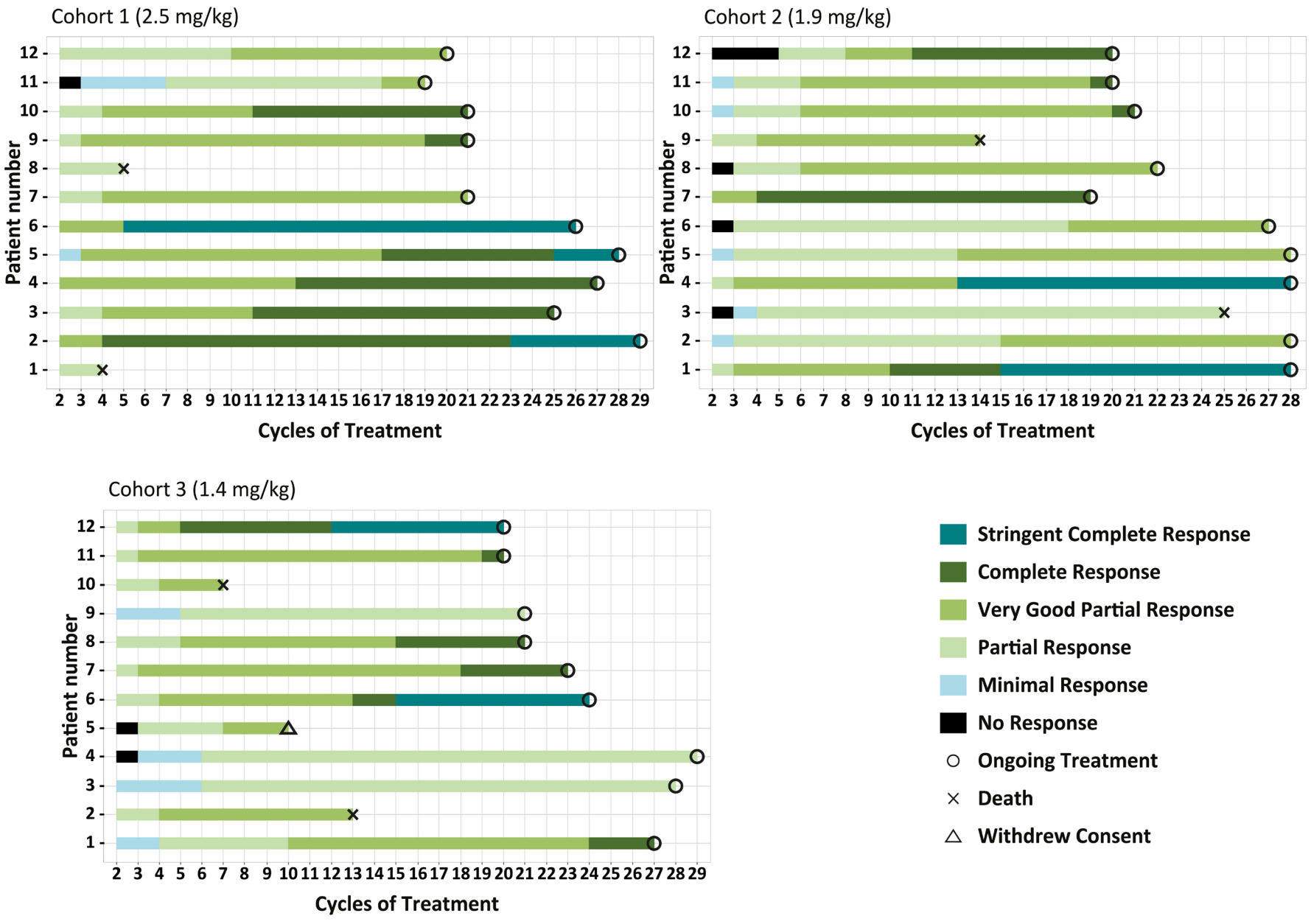


Figure 3. Swimmer plot showing response evolution during treatment per patient.

In a frailty subgroup analysis of the MAIA trial, the ORR of intermediate-fit and frail patients receiving the DaraRd triplet was 96.9% and 87.2%, respectively. More specifically, a CR or better was achieved in 53.9% and 43.6% and a VGPR or better in 84.4% and 74.4% of intermediate-fit and frail patients, respectively. In a median follow-up of 36.4 months, PFS was not reached for the intermediate-fit and frail subgroups.[6] Interestingly, the rates of CR or better and VGPR and better in the MAIA trial in the intermediate-fit and frail subgroups are comparable to those achieved in our study.

VRd is another regimen which is commonly used in the upfront treatment of transplant-ineligible patients with NDMM based on the results of the SWOG S0777 study.[2] The ORR was 90% and the VGPR or better rate reached 75%. Although the PFS and the OS were prolonged compared with those achieved with Rd in the subset of patients who did not receive an ASCT, the OS benefit did not reach statistical significance in patients aged 65 years or older. Overall, belamaf-Rd has similar efficacy to DaraRd and VRd, whereas it allows for less frequent hospital visits. Furthermore, belamaf-related ocular toxicity seems to be completely reversible in contrast to bortezomib-related peripheral neuropathy which may not resolve completely in the long term.

In our study, the belamaf-Rd combination produced deep and durable responses, with a very short time to first response, across all cohorts. Most patients received belamaf at the q12w interval, as most experienced at least one grade ≥2 OAE. Importantly, this extended dosing schedule had minimal impact on patients' vision, as manifested by the low frequency of clinically meaningful declines in BCVA. Additionally, grade ≥3 keratopathy was identified in <2% of assessments and resolved in a very short time. In contrast, keratopathy rates ranged from 32% to 72% across clinical trials and real-world studies in heavily pretreated RRMM patients who received belamaf monotherapy.[19-23,34] However, the lowest reported rates in real-world studies should be interpreted with caution, because patients' adherence to monthly ophthalmological assessments and ophthalmological expertise may differ significantly among studies. Furthermore, considering the pattern of development of belamaf-associated keratopathy,[34] we estimate that the clinical manifestation of keratopathy follows the temporal pattern of eye itching when keratopathy is grade ≤1, while visual acuity declines when keratopathy progresses to grade ≥2. Thus, withholding belamaf dosing at the first sign of a grade ≥2 OAE, and restarting when all OAE are grade ≤1, as was done in our study, significantly lowers the risk of developing visual impairment. This was particularly evident for the q12w schedule.

Despite the occurrence of ocular symptoms, daily functioning was not significantly impaired. Indeed, "all/most of the time" worst responses in the activities of daily living category, including driving, reading, working with a computer or bank machine and watching television, ranged between 1.5-3%. Apparently, a distinction should be made between clinically significant and asymptomatic ocular toxicity in order to make treatment decisions about belamaf administration, in analogy to bortezomib-related peripheral neuropathy. Questions on ocular symptoms and impact on activities such as driving, reading, watching television or using a smartphone, are validated and reliable, they include essential psychometric properties and can serve as an endpoint in clinical research.[35,36]

Another safety signal in our study was the occurrence of respiratory tract infections, especially COVID-19, at a higher frequency than in other clinical trials evaluating belamaf-based regimens.[18,24,25] We assume that the increased infection rate can be partially attributed to the COVID-19 pandemic. However, the rate of grade 3-4 infections in our study is very low compared to that in studies of BCMA-targeting bispecific antibodies, such as teclistamab and erlanatamab (8.3% *vs.* 44.8% and 39.8%, respectively).[37,38] B-cell depleting therapies impair the host's humoral response to infections.[39] Lymphopenia and natural killer-cell depletion with anti-CD38 treatment predispose to severe and atypical infections such as listeria.[40-42] The increased infection risk with novel immunotherapies is multifactorial and may be associated with hypogammaglobulinemia, neutropenia, lymphopenia, and T-cell exhaustion.[43,44] Furthermore, patients under treatment with these agents are less likely to have an optimal humoral response to vaccination against common pathogens, including severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), also considering the deregulated immune response due to the underlying myeloma.[45-48] Complete vaccination is essential to prevent severe infections.[49] Finally, the role of dexamethasone should also be revisited. We note that the cumulative dexamethasone dose is greater in our study than in the monotherapy belamaf studies in the RRMM setting, which may have a synergistic effect on the increased risk of infections. In a recent study, a dose/schedule-adjusted Rd-R regimen was compared to continuous Rd in intermediate-fit, elderly NDMM patients.[50] In the comparator arm, dexamethasone was discontinued after nine Rd cycles, without any compromise in clinical activity. A limited duration of intensified therapy followed by a maintenance phase seems a reasonable approach, although there are currently no data to challenge the standard of continuous treatment in non-transplant eligible patients with NDMM. Consequently, prompt implementation of supportive medications to reduce the risk of infections is of utmost importance. In our study, all patients received valacyclovir for varicella zoster virus prophylaxis, trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* prophylaxis and levofloxacin for the first 3 months of treatment. Furthermore, all patients were advised to undergo annual influenza, pneumococcal and SARS-CoV-2 vaccination. Supportive care also included gastroprophylaxis and antithrombotic prophylaxis, while preventive measures were applied to re-

duce the risk of OAE: from treatment initiation, all patients received preservative-free artificial tears at least four to eight times daily, while they were instructed to use a cooling eye mask for up to 4 hours during belamaf administration (see *Online Supplementary Information*). Following the results of part 1 of the study, intravenous or subcutaneous immunoglobulin infusions are to be administered to all patients who manifest hypogammaglobulinemia during the course of the study until their IgG levels are >400 mg/dL. In conclusion, the clinical activity of the belamaf-Rd triplet was very promising, as rapid, deep and durable responses were observed across all doses. Treatment-emergent AE were manageable with appropriate supportive care. Furthermore, the lower dose levels of 1.9 and 1.4 mg/kg provided an optimal balance between OAE and clinical activity, especially at the q12w dosing interval. To further reduce the risk of ocular events, hematologists should remain vigilant and withhold belamaf if a patient manifests a grade ≥2 OAE; the drug can be restarted when all OAE subside to grade ≤1. These results suggest that this novel combination may be an effective treatment option for transplant-ineligible NDMM patients.

Disclosures

ET has received honoraria for advisory board participation or lectures from Amgen, AstraZeneca, Bristol Myers Squibb, Eusa Pharma, GSK, Integris Pharma, Janssen, Pfizer, Sanofi, and Takeda; research support (to his institution) from Amgen, GSK, Janssen, Sanofi, and Takeda; and travel grants from Amgen, Eusa Pharma, and Takeda. MG declares honoraria from GSK, Janssen, Sanofi, AbbVie, Amgen, and Takeda. EK declares honoraria and research funding from Amgen, Janssen, GSK, and Pfizer. MAD declares honoraria from AbbVie, Amgen, Bristol Myers Squibb, GSK, Janssen, Karyopharm, Pharmacyclics Inc, Pfizer, Sanofi, and Takeda. SG is an employee of Health Data Specialists, Dublin, Ireland. All other authors have no conflicts of interest to disclose.

Contributions

ET and MAD conceived and supervised the study. ET, MG, and SG were responsible for the methodology and SG for the formal analysis. ET, MG, INS, PM, DF, MM, FT, VS, IVK, OT, RS, EEP, EK, and MAD performed the investigation. ET and MG wrote the original draft of the manuscript. INS, PM, DF, MM, FT, VS, RS, EEP, SG, IVK, OT, EK, and MAD reviewed and edited the manuscript. All authors read and agreed to the published version of the manuscript.

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Data-sharing statement

Primary data are available upon reasonable request from the corresponding author.

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