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

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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.

[3]Health Data Specialists, Dublin, Ireland.

Correspondence: Evangelos Terpos, MD, PhD, Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Alexandra General Hospital, 80 Vas. Sofias Avenue, 11528, Athens, Greece; Tel.: +30-213-216-2846; Fax: +30-213-216-2511; Email: eterpos@med.uoa.gr

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Author contributions

Conceptualization, ET and MAD; methodology, ET, MG, SG; formal analysis, SG; investigation, ET, MG, INS, PM, DF, MM, FT, VS, IVK, OT, RS, EEP, EK, MAD; writing—original draft, ET and MG; writing—review and editing, INS, PM, DF, MM, FT, VS, RS, EEP, SG, IVK, OT, EK, MAD; supervision, ET and MAD. All authors have read and agreed to the published version of the manuscript.

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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 25mg on days 1-21 every 28 days and dexamethasone 40mg weekly (belamaf-Rd) in transplant ineligible patients with newly diagnosed multiple myeloma. 36 patients (median age 72.5 years) were randomized to receive belamaf at three different doses (2.5/1.9/1.4 mg/kg) every 8 weeks (q8w). Dosing schedule was extended to every 12 weeks (q12w) to account for ocular toxicity. Most common ≥ Grade (Gr) 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%). Gr 3-4 ocular adverse events (OAEs), comprising of visual acuity decline from baseline and/or keratopathy, were reported in 39/216(18.1%)/ 33/244(13.5%)/ 26/207(12.6%) ophthalmological assessments in cohorts 2.5/1.9/1.4 mg/kg. Importantly, Gr 3-4 keratopathy was identified in 9/216 (4.2%)/ 1/244(0.4%)/ 1/207(0.5%) assessments. Most patients (32/36, 88.9%) were treated in the extended q12w schedule, where dose holds due to OAEs were 40, 33 and 16 in cohorts 2.5/1.9/1.4. Overall, ≥VGPR and ≥CR rates were 83.3% and 52.8%, without significant differences among cohorts. Over a median follow-up of 20.3 months no disease progression was reported; 6 patients discontinued treatment due to infection-related death (n=4 COVID-19, n=2 pneumonia) and 1 patient withdrew consent. Based on toxicity/efficacy balance, the recommended phase 2 dose was 1.9 mg/kg q8w, extended to q12w for toxicity. Belamaf-Rd, with the extended schedule for belamaf, has shown important clinical activity and a significant improvement of OAEs with minimal impact on vision-related functioning in an elderly, non-transplant eligible population.

Keywords: multiple myeloma; newly diagnosed; transplant-ineligible; belantamab mafodotin; lenalidomide; dexamethasone; frail; safety; efficacy

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 of 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 (TI) NDMM.[1]

The reported median progression-free survival (PFS) for 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 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 DaraRd in the MAIA study.[4] DaraVMP and DaraRd have improved patient outcomes compared to VMP and Rd, respectively, regardless of frailty status; however, frail patients had inferior survival outcomes compared with non-frail patients in both ALCYONE and MAIA studies.[5,6] Therefore, new treatment approaches need to be explored to further optimize outcomes in this patient population, especially for frail patients that also have high-risk disease and, by extent, poor prognosis,[7] considering also the debatable cost-effectiveness of adding anti-CD38 monoclonal antibodies in the first-line.[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 (ADCs), bispecific antibody constructs, and chimeric antigen receptor-modified T-cell therapy.[13] Ongoing trials evaluate each of these treatment strategies in the first line setting.[14-16] Belantamab mafodotin (belamaf; GSK2857916) is a first-in-class ADC, which comprises of a humanized IgG1κ monoclonal antibody and the cytotoxic agent monomethyl auristatin F (MMAF).[17] Belamaf has demonstrated important efficacy in heavily pre-treated patients with relapsed/refractory MM (RRMM) and ≥4 prior lines of treatment.[11,12] In the DREAMM-2 study, belamaf monotherapy was administered at 2.5 mg/kg every three 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 versus 7 months, respectively, p=0.56) in the DREAMM-3 study including RRMM patients with 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. Although cross trial comparisons should be made with caution, it seems that belamaf has a lower infection risk overall compared with anti-myeloma immunotherapies such as bispecific antibodies.[13]

Additionally, the efficacy of belamaf increases substantially in combination with other anti-myeloma agents, as in such cases a synergic 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 VGPR or better.[24] Similarly, the combination of belamaf, carfilzomib and dexamethasone produced a ≥VGPR response in 60% of relapsed patients who had received ≥1 line 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 who are not eligible for ASCT in the phase 1/2 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 TI NDMM patients.

The main objective of Part 1 of the BelaRd study was to establish the RP2D of belamaf in combination with standard dose Rd in transplant ineligible patients with NDMM. 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 (DLTs), the number of participants with adverse events (AEs) and serious adverse events (SAEs), along with the evaluation of preliminary clinical activity, in each of the three dosing cohorts.

Methods

Patient selection

Key eligibility criteria are shown in the Supplement (**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.

Study design and intervention

The study is divided into two parts. Part 1 focuses 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 recommended phase 2 dose (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 for 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 to every 12 weeks (q12w) depending on toxicity. More specifically, if at least one ≥Grade (Gr) 2 ocular adverse event (OAE) is observed, belamaf dosing is held, and restarted when all OAEs are ≤Gr1. From that point forward, all subsequent belamaf doses are rescheduled to q12w. OAEs are defined as Snellen Best corrected visual acuity (BCVA) decline from baseline and/or corneal findings suggestive of keratopathy.

Lenalidomide is administered at 25mg po for 21 days in each 28-day cycle of treatment and dexamethasone at 40mg po is administered weekly, according to the approved Rd regimen. Patients aged 75 years or older started dexamethasone at 20mg weekly, whereas patients with renal impairment at baseline started with reduced lenalidomide dose. Lenalidomide and dexamethasone dose levels were adjusted according to the highest grade of hematologic and

non-hematologic toxicity attributed to each drug (Supplemental file). Lenalidomide dose levels included 25mg, 20mg, 15mg, 10mg, 5mg, whereas dexamethasone dose levels included 40mg, 20mg, 12mg, 8mg, 4mg.

All NDMM patients enrolled in the study receive appropriate antiviral, antibiotic and antithrombotic prophylaxis as per standard clinical practice. Infection prevention included po valacyclovir 500mg daily for varicella zoster virus, po trimethoprim/sulfamethoxazole 800/160mg three times weekly for pneumocystis carinii and po levofloxacin 500mg daily during the first three months of treatment. Additionally, patients were instructed to get vaccinated for COVID-19, streptococcus pneumoniae and influenza.

Study outcomes and assessments

DLTs were evaluated during the first cycle of treatment and included the AEs shown in the Supplement (**Table S2)**.

During Part 1, ocular safety was closely monitored through several assessments, including ophthalmological examination performed at baseline, every 4 weeks (before the initiation of each cycle of treatment) and as clinically indicated. Ocular symptoms, BCVA assessment and slit lamp corneal evaluation were assessed. Evaluation of the lens, fundoscopic examination and intraocular pressure measurement were performed as required. In addition, the Ocular Surface Disease Index (OSDI) was used to measure dry eye disease and its impact on Activities of Daily Living (ADL). OAEs were graded by the Keratopathy Visual Acuity scale, while ocular symptoms and all non-ocular AEs were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Efficacy assessments were performed on day 1 of each 28-day cycle. Overall Response Rate (ORR) was defined as the percentage of participants with a confirmed partial response

(PR), very good partial response (VGPR) and (stringent) complete response [(s)CR] according to the IWMG response criteria.[26-28]

Further information on methodology is provided in the Supplement.

Results

Patient 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), whereas 19 patients (52.8%) were males. Regarding Eastern Cooperative Oncology Group (ECOG) performance status (PS) at baseline, 15 (41.7%) patients had ECOG PS 0, 19 (52.8%) ECOG PS 1 and 2 (5.6%) ECOG PS 2. According to the IMWG frailty score, 32 (88.9%) patients were characterized as intermediate-fit and 4 (11.1%) patients as frail. The patient disposition according to prognostic staging systems was n=11 (30.6%), n=19 (52.8%), n=6 (16.7%) for international staging system (ISS) 1, 2 and 3, respectively, and n=6 (16.7%), n=27 (75.0%), n=3 (8.3%) for revised ISS 1, 2 and 3, respectively. 27 (75.0%) patients had IgG myeloma, 7 (19.4%) had IgA myeloma and 2 (5.6%) patients had light chain myeloma. Patient 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 ≥1 dose hold due to AEs. The proportions of patients with a ≥1 dose hold in cohorts 2.5/1.9/1.4 were 8 (66.7%)/11 (91.7%)/12 (100%). All dose holds were due to OAEs. At the cut-off date, 29 (80.6%) patients were still on treatment, while 7 (19.4%) had discontinued: 6 due to infection-related death (COVID-19: 1/1/2; Pneumonia: 1/1/0, for cohorts 2.5/1.9/1.4 respectively) and 1

withdrew consent due to personal reasons related to inability to visit the hospital according to the study protocol.

Dose intensity (DI, mg/kg/Q4W) for each patient was defined as the total belamaf administrated in mg/kg divided by the overall number of cycles per patient. For cohorts 2.5/1.9/1.4 mg/kg, the intended DI was 1.25/0.95/0.70, while the median DI observed was 0.82/0.65/0.50, respectively.

RP2D selection

After reviewing all the safety and efficacy data, the safety review committee of the study concluded to the RP2D of belamaf at 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 as, compared to the higher dose of 2.5 mg/kg, equally deep responses and fewer OAEs are reported.

Safety

OAEs, including BCVA decline from baseline and keratopathy, were reported in 191/216 (88.4%), 200/244 (82.0%), 168/207 (81.2%) ophthalmological assessments in the three cohorts, respectively (**Table 2**), while ≥Gr3 OAEs were reported in 39/216 (18.1%), 33/244 (13.5%) and 26/207 (12.6%) of assessments. The median times to the first ≥Gr2 OAE were 3.9, 4.5 and 5.9 months, for cohorts 2.5, 1.9 and 1.4 mg/kg, respectively. Among 216/244/207 ophthalmological assessments in cohorts 2.5/1.9/1.4 mg/kg, a meaningful decline in BCVA (BCVA <20/50) with at least 3 lines drop in the better seeing eye was observed in 21 (9.7%)/24 (9.8%)/17 (8.5%), with median times to resolution 1.2, 1.4 and 1.6 months, respectively. Additionally, BCVA ≤20/200 with at least 3 lines drop in the better seeing eye was noted in only 2 (0.9%)/3 (1.2%)/8 (3.9%). Keratopathy of any grade was

evident in 136/216 (63.0%), 130/244 (53.3%) and 94/207 (45.4%) assessments, while ≥Gr3 keratopathy was noted in 11/667 (1.6%), 9 of which were reported in cohort 2.5. Across all cohorts, the most frequently reported ≥Gr3 ocular symptom was visual impairment (26/665, 3.9%). Regarding OSDI, from 202/234/196 responses received, the number 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 6 (3.0%)/6 (2.6%)/8 (4.1%), while the respective proportions in the ADL category (reading, driving at night, working with a computer or bank machine, watching TV) were 6 (3.0%)/4 (1.7%)/3 (1.5%), for cohorts 2.5/1.9/1.4. 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 held (delayed or skipped) in 134 assessments out of 386 planned infusions (34.7%) in both Q8W and Q12W schedules due to OAEs, while ≥Gr 2 OAE were reported for all patients that transitioned from the Q8W to the Q12W schedule. In the extended q12w schedule, dose holds were reported in 58.0% (40/69), 40.3% (33/82), and 30.8% (16/52) assessments, in cohorts 2.5/ 1.9/ 1.4, respectively. Importantly, the percentage of doses skipped in the 2.5 cohort was twice the percentage of doses skipped in the 1.4 cohort. Moreover, the median delay for belamaf re-administration following an OAE-related dose hold were 8.0/4.4/4.6 weeks for cohorts 2.5/ 1.9/ 1.4, respectively, reflecting a substantial difference in terms of ocular safety.

DLTs were reported in 8 patients: 2/4/2 in cohorts 2.5/1.9/1.4, respectively, and included fatigue Gr3 (n=6) and rash Gr3 (n=2) (**Table 3**). No hematological or ocular DLTs emerged. The most common (affecting ≥15% of the patients) non-ocular ≥ Gr3 treatment-emergent AEs (TEAEs), overall and in each dosing cohort, were as follows: fatigue [n=21, 58.3%; 7 (58.3%)/7 (58.3%)/7 (58.3%)], rash [n=6, 16.7%; 2 (16.7%)/2 (16.7%)/2 (16.7%)], diarrhea [n=8, 22.2%; 2 (16.7%)/3 (25.0%)/3 (25.0%)] and COVID-19 infection (n=5, 13.9%; 2

(16.7%)/1 (8.3%)/2 (16.7%)] (**Table 3**). Regarding ≥ Gr3 infections other than COVID-19, pneumonia was reported for 3 patients (one in each cohort, 8.3%) and lower respiratory tract infection for one patient in cohort 3. SAEs were reported in 5 (41.7%), 2 (16.7%) and 4 (33.3%) patients in cohorts 2.5/1.9/1.4 mg/kg. There were 6 infection-related fatal events; 4 patients died due to COVID-19 (1/1/2 in cohorts 2.5/1.9/1.4) and 2 patients due to pneumonia (1/1/0 in cohorts 2.5/1.9/1.4). Furthermore, no ≥Gr3 thrombocytopenias and infusion-related reactions were reported.

Hypogammaglobulinemia (IgG < 400 mg/dl) was a common finding during the study, manifesting in 27/36 (75.0%) patients, while severe hypogammaglobulinemia (IgG < 200 mg/dl) manifested in 14/36 (38.9%) patients. In order to decrease the risk for 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, CR or better was achieved in 7 (58.3%)/ 6 (50.0%)/ 6 (50.0%), VGPR or better in 10 (83.3%)/ 11 (91.7%)/ 9 (75.0%) and PR in 2 (16.7%)/1 (8.3%)/ 3 (25.0%) of the patients in cohorts 2.5/1.9/1.4 mg/kg. The median (range) times to first response were 1.1 (1.0-2.1)/1 (0.9-3.8)/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)/8.0 (2.8-24.8) months for the respective cohorts. In the subgroup of frail patients (4/36, 11.1%), sCR/VGPR/PR was manifested in 1/2/1 patients. In the subgroup of patients with ≥2 cytogenetic abnormalities (4/36, 11.1%), sCR/VGPR was manifested in 2/2 patients.

After a median follow-up of 20.3 months, no disease progression was observed, median PFS, median TTP and median OS were not reached, and responses continue to deepen across

all cohorts. The KM curve for PFS and TTP 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 response and were evaluated for minimal residual disease (MRD) using next-generation flow, 14 (73.7%) were MRD negative at the 1×10^{-5} sensitivity level, accounting for 6 (85.7%), 5 (83.3%) and 3 (50%) patients in cohorts 2.5, 1.9 and 1.4, respectively.

Discussion

The triplet combination of belamaf-Rd demonstrated tolerability and sustainable efficacy in the treatment of TI NDMM patients, in a less intensified dosing scheme for belamaf compared to the monotherapy dosing schedule of 2.5 mg/kg q3w 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 ≥Gr2 OAEs, without compromising efficacy.[29] For this reason, studies investigating belamaf combinations are designed with lower dose intensity than DREAMM-2, in order to reduce both ocular and non-ocular additive toxicity.[30-32] Similarly, we designed 3 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 for OAEs in this frail population, the dosing interval was extended to q12w in the first sign of a ≥Gr2 OAE. In the q12w interval, fewer dose holds were observed in the 1.9 and 1.4 cohorts compared to the 2.5 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 cohorts compared to the 1.4 cohort. Taking this into account and considering the high patient variability in terms of toxicity, we decided to select the 1.9 cohort as the RP2D.

There are two ongoing studies evaluating belamaf-VRd in NDMM patients. The phase 1 DREAMM-9 study evaluates the combination in different belamaf dose levels and dosing frequency in TI NDMM patients.[16] In all cohorts, belamaf is administered at more extended time intervals after 8 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, 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 was 100%/92% in cohorts 1.9/1.4 mg/kg. VGPR or better was observed in 92%/85% and 100%/91% in cohorts 1.9/1.4, at the intervals of 3/4 and 6/8 weeks, respectively. In our study, VGPR or better was achieved in 92%/75% of patients in cohorts 1.9/1.4 at an extended belamaf schedule. Additionally, in frail patients and patients with 2 or more cytogenetic abnormalities, 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 the part 2 phase 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 in the study treatment of DREAMM-9 a proteasome inhibitor is included. Additionally, GEM-BELA-VRd study evaluated the combination of belamaf at 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 4 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 the PFS2. Although there are limited data showing a potentially reduced activity of anti-BCMA CAR T-cell immunotherapy following anti-BCMA treatment, the sequence of the available drug combinations may play a key role.

In a frailty subgroup analysis of the MAIA trial, intermediate and frail patients receiving the DaraRd triplet achieved an ORR of 96.9% and 87.2%, respectively. More specifically, ≥CR was achieved in 53.9% and 43.6% and ≥VGPR in 84.4% and 74.4% of intermediate and frail patients, respectively. In a median follow-up of 36.4 months, PFS was not reached for the intermediate and frail subgroup.[6] Interestingly, the ≥CR and ≥VGPR rates achieved in MAIA trial in the intermediate and frail subgroups are comparable to the ≥CR and ≥VGPR rates 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 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, 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 ≥Gr2 OAE. Importantly, this extended dosing schedule had minimal impact on patients' vision, as manifested by the low frequency of clinically meaningful decline in BCVA. Additionally, ≥Gr3 keratopathy was identified in

<2% of assessments with a very short resolution time. On the contrary, 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 interpretated with caution, because the patient adherence to monthly ophthalmological assessments and the 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 ≤Gr1, while visual acuity declines when keratopathy progresses to ≥Gr2. Thus, holding belamaf dosing at the first sign of a ≥Gr2 OAE, and restarting when all OAEs are ≤Gr1, as was done in our study, significantly ameliorates the risk of developing visual impairment. This was particularly evident in the q12w schedule.

Ocular symptoms continued to manifest. However, daily functioning was not significantly impaired. Indeed, "all/most of the time" worst responses in the ADL category, including driving, reading, working with a computer or bank machine and watching TV, ranged between 1.5-3%. Apparently, we need to distinguish between clinically remarkable 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 like driving, reading, watching TV 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 is the occurrence of respiratory tract infections, especially due to COVID-19, in a greater frequency than in other clinical trials evaluating belamaf-based regimens.[18,24,25] We assume that the increased infection rate can partially be attributed to the COVID-19 pandemic. However, compared to BCMA-targeting bispecific

antibodies, such as teclistamab and erlanatamab, the rate of Gr 3-4 infections in our study is very low (8.3% vs 44.8% and 39.8%, respectively).[37,38] B-cell depleting therapies impair the host humoral response to infections.[39] Lymphopenia and natural killer cell depletion with anti-CD38 treatment predispose for severe and atypical infections such as listeria.[40-42] The increased infection risk with the 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 SARS-CoV-2, considering also 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 should note that the cumulative dexamethasone dose is greater in our study compared with 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-fil, elderly NDMM patients.[50] In the comparator arm, dexamethasone was discontinued after 9 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 consulted to receive annual flu, pneumococcal and SARS-CoV-2 vaccination. Supportive care included also gastroprophylaxis and antithrombotic prophylaxis, while

preventive measures were applied to reduce the risk of OAEs: 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 four hours during belamaf administration (see supplementary information). Following the Part 1 results of the study, intravenous or subcutaneous immunoglobulin infusions have to be administered in all patients that manifest hypogammaglobulinemia during the course of the study until IgG >400mg/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. TEAEs are manageable with appropriate supportive care. Furthermore, the lower dose levels of 1.9 and 1.4 mg/kg achieve an optimal balance between OAEs and clinical activity, especially in the q12w dosing interval. Moreover, to further reduce the risk of ocular events, hematologists should remain vigilant to hold belamaf when a ≥Gr2 OAE manifest, and restart when all OAEs subside to ≤Gr1. These results suggest that this novel combination may be an effective treatment option for TI NDMM patients.

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Table 1 Patient 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	8 (66.7)	5 (41.7)	6 (50.0)
Female	4 (33.3)	7 (58.3)	6 (50.0)
ECOG PS, n (%)			
0	4 (33.3)	3 (25.0)	8 (66.7)
1	6 (50.0)	9 (75.0)	4 (33.3)
2	2 (16.7)	0 (0.0)	0 (0.0)
ISS, n (%)			
I	4 (33.3)	3 (25.0)	4 (33.3)
II	5 (41.7)	7 (58.3)	7 (58.3)

III	3 (25.0)	2 (16.7)	1 (8.3)
R-ISS, n (%)			
I	1 (8.3)	2 (16.7)	3 (25.0)
II	9 (75.0)	10 (83.3)	8 (66.7)
III	2 (16.7)	0 (0.0)	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 (%)	1 (8.3)	2 (16.7)	0 (0.0)
17p13	0 (0.0)	0 (0.0)	0 (0.0)
t (4;14)	0 (0.0)	2 (16.7)	0 (0.0)
t (14;16)	1 (8.3)	0 (0.0)	0 (0.0)
IMWG Frailty Score, n (%)			
Fit (score=0)	0 (0.0)	0 (0.0)	0 (0.0)
Intermediate-fitness (score=1)	10 (83.3)	11 (91.7)	11 (91.7)
Frail (score ≥ 2)	2 (16.7)	1 (8.3)	1 (8.3)

[a] High risk cytogenetics defined as Del 17p13, t(14:16) or t(4:14)

ECOG PS, Eastern Cooperative Oncology Performance Status; ISS, International Staging System; R-ISS, Revised International Staging System; IMWG, international myeloma working group; Q8W, every 8 weeks

Table 2 Ocular adverse events and time to resolution

	Cohort 1 (2.5 mg/kg Q8W)	**Cohort 2 (1.9 mg/kg Q8W)**	**Cohort 3 (1.4 mg/kg Q8W)**
Total number of OAEs[a] /Total number of ocular assessments (%)	**216**	**244**	**207**
Grade 0-1	86 (39.3%)	130 (55.7%)	115 (56.5%)
Grade 2	91 (43.9%)	81 (31.1%)	66 (31.4%)
Grade 3-4	39 (18.1%)	33 (13.5%)	26 (12.6%)
Total number of BCVA decline assessments/Total number of ocular assessments (%)	**216**	**244**	**207**
Grade 0-1	90 (41.7%)	139 (57%)	119 (57.5%)
Grade 2	93 (43%)	73 (30%)	63 (30.4%)
Grade 3-4[b]	33 (15.3%)	32 (13%)	25 (12.1%)
Total number of keratopathy assessments/Total number of ocular	**216**	**244**	**207**

assessments (%)			
Grade 0-1	179 (82.9%)	214 (87.3%)	185 (89.4%)
Grade 2	28 (13.0%)	30 (12.2%)	21 (10.1%)
Grade 3-4	9 (4.2%)	1 (0.4%)	1 (0.5%)
Number of assessments with Meaningful BCVA decline[c] with at least 3 lines drop in the better seeing eye/Total number 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 OAEs 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	2.1 (0.3-6.3)	1.9 (0.9-6.2)	1.9 (0.9-8.6)

months, median (range)			
Time to resolution[d] 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 in this analysis describe assessments of decreased BCVA from baseline (C1D1) and assessments of keratopathy. These assessments are graded by the Keratopathy Visual Acuity scale. In each assessment, the maximum grade of the aforementioned is presented.

[b]No BCVA change grade 4 was observed

[c]Meaningful BCVA decline is defined as BCVA decrease worse than 20/50 at the better-seeing eye. Better seeing eye was considered the eye that presented higher visual acuity at baseline (based on BCVA). Patients with BCVA worse than 20/50 in both eyes at baseline are excluded from this analysis.

[d]For meaningful BCVA decline with at least 3 lines drop in better seeing eye, resolution was considered when BCVA became 20/50 or better, or the decline was less than 3 lines drop; while for the resolution of OAEs, BCVA decline and keratopathy; resolution was considered when grade became ≤ 1.

OAE, ocular adverse events; BCVA, best corrected visual acuity; Q8W, every 8 weeks

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						
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						
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%)
Diarrhoea	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)			
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 visual acuity deterioration; it corresponds to the following MedDRA terms: vision blurred, visual acuity reduced and visual impairment. The worst grade of the aforementioned terms is presented.

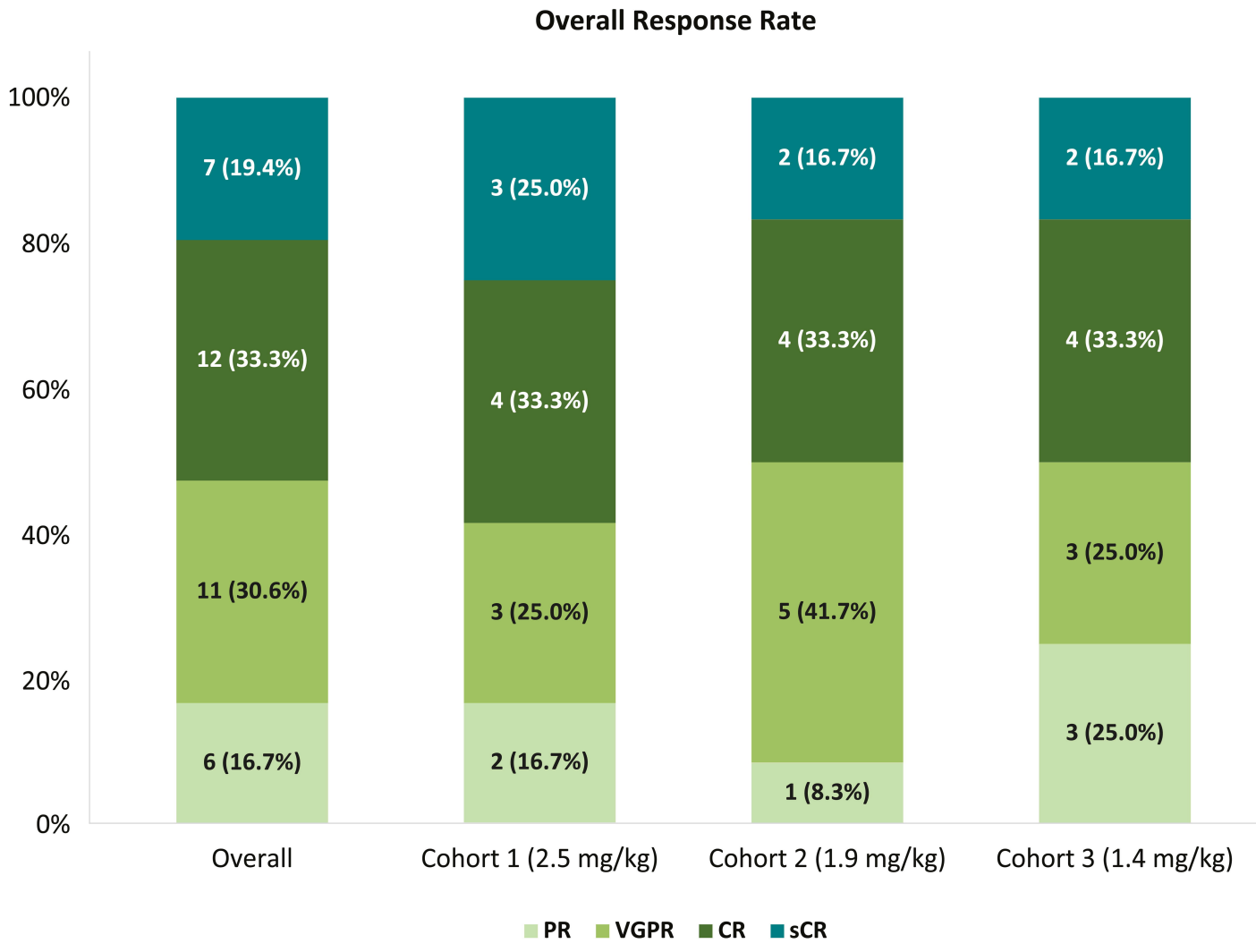
MedDRA, Medical Dictionary for Regulatory Activities; Q8W, every 8 weeks

Figure legends

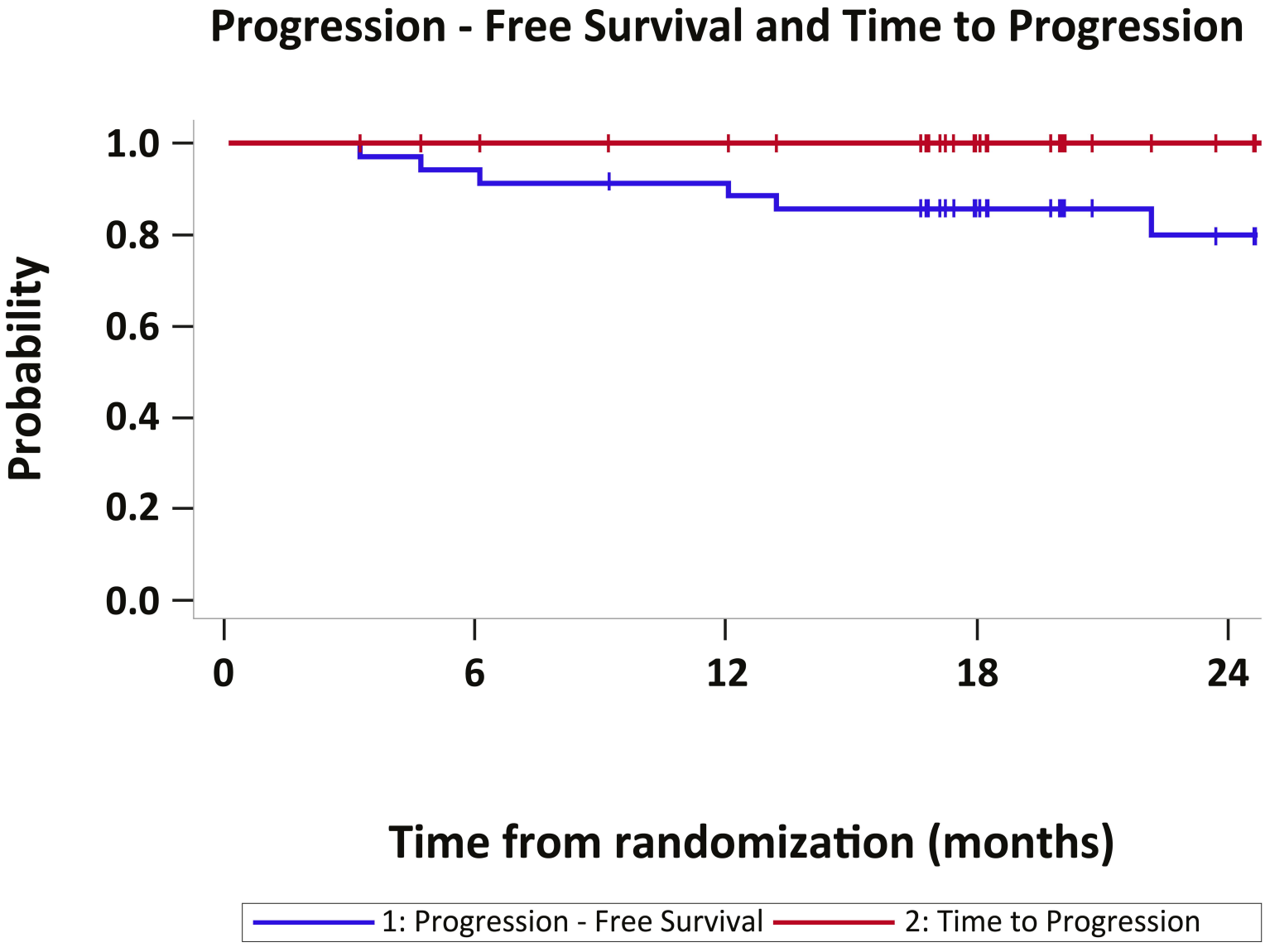
Figure 1. Overall response rate and time to response. Abbreviations: CR, complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Figure 2. Progression-Free Survival and Time to progression

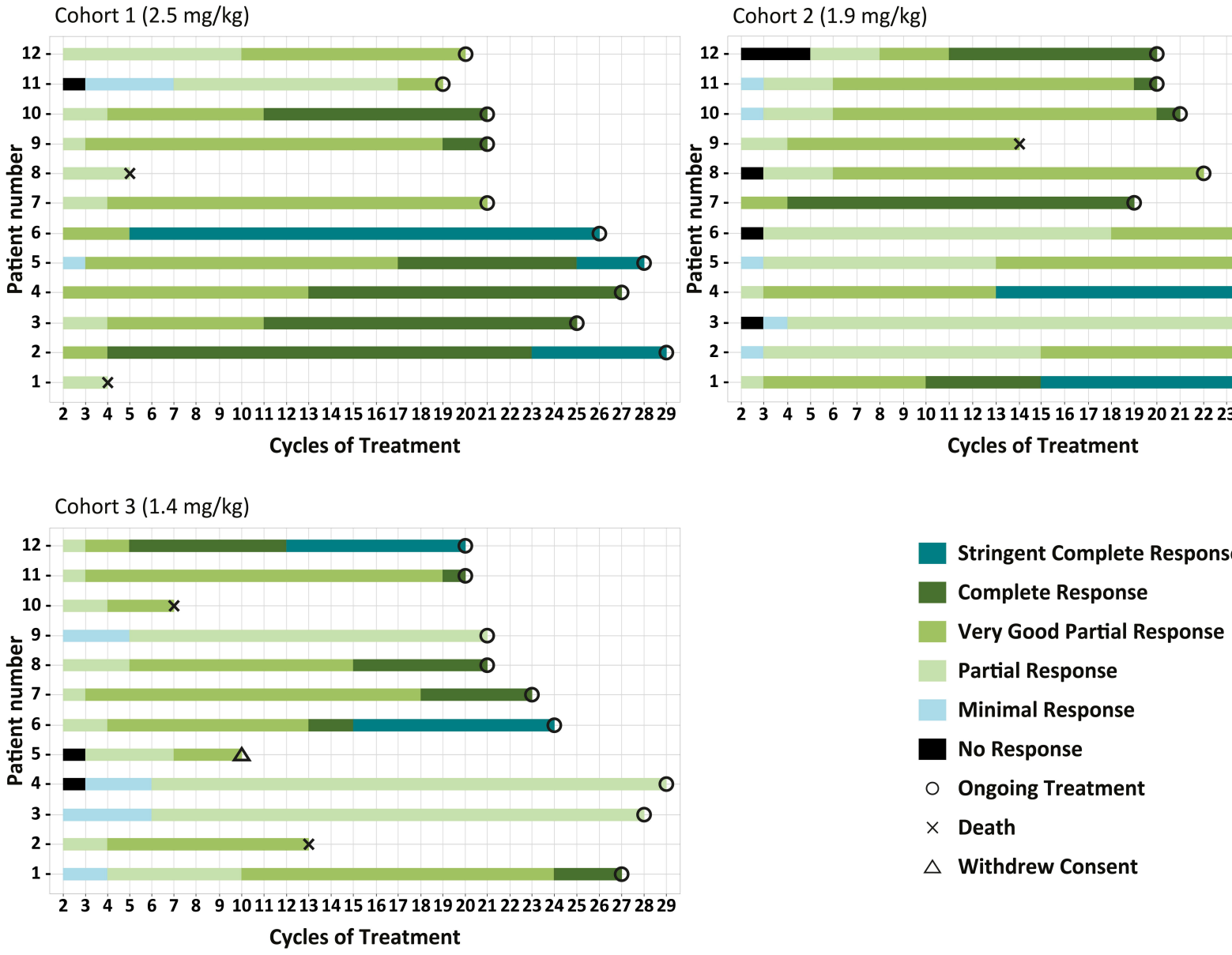
Figure 3. Swimmer's plot showing response evolution during treatment per patient



	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)



At risk	36	34	32	22	12
At risk	36	34	32	22	12


Cohort 1 (2.5 mg/kg)
Patient number
Cycles of Treatment
Cohort 2 (1.9 mg/kg)
Patient number
Cycles of Treatment
Cohort 3 (1.4 mg/kg)
Patient number
Cycles of Treatment
Stringent Complete Response
Complete Response
Very Good Partial Response
Partial Response
Minimal Response
No Response
Ongoing Treatment
Death
Withdrew Consent

Supplementary methods

Time to endpoints

All time to event endpoints were calculated from the time of randomization. Progression-free survival (PFS) was calculated until the date of disease progression or death from any cause, whichever occurred first. Time to progression (TTP) was calculated until the date of myeloma progression, whereas overall survival (OS) was calculated until the date of death due to any cause. Patients who did not experience any event at the time of the analysis were censored at the date of their last available disease assessment denoting absence of progression (for PFS/TTP) or last follow-up (for OS).

Statistical analysis

No formal statistical hypothesis was to be tested for this study; therefore, no sample size calculation was performed. The analysis is based on descriptive statistics. Categorical variables are expressed with absolute and relative frequencies, while the continuous ones were described with median (range) or mean with standard deviation. For the PFS and TTP estimates, survival analysis techniques were employed using the Kaplan-Meier (KM) method. As per protocol, the analysis is performed in the dose limiting toxicity (DLT) population. This is defined as all patients who had received ≥1 belamaf dose and who were followed up for ≥4 weeks or patients who could not be followed up for ≥4 weeks due to toxicity reasons (i.e., death/treatment discontinuation). As per study design, for patients who received ≥1 belamaf dose but were not part of the DLT population, a new patient was enrolled in replacement; safety data of the replaced patients were to be analyzed separately, however, no such patients exist. Statistical analysis was conducted using SAS (version 9.4). The data cut-off date for this analysis was June 5th, 2023. All authors had access to primary clinical trial data.

Data Sharing Statement

Individual participant data will not be shared until the final analysis of the phase 2 portion of the BelaRd study. The study protocol is uploaded separately.

Table S1 Key patient eligibility criteria

Inclusion criteria
Age ≥18 years old
Multiple myeloma diagnosis according to the International Myeloma Working Group (IMWG) criteria (CRAB-SLiM criteria)[26]
Measurable disease, defined as at least one of the following: • Urine M-protein excretion ≥200 mg/24h • Serum M-protein concentration ≥0.5 g/dL • Involved serum free light chain (sFLC) level ≥10 mg/dL, with an abnormal sFLC ratio (<0.26 or >1.65)
Eastern Cooperative Oncology Group performance status of 0 to 2
Adequate organ function, defined as follows: • Absolute neutrophil count ≥1.5 × 10^9/L without granulocyte colony-stimulating factor support • Hemoglobin ≥ 8.0 g/dL • Platelet count ≥75 x 10^9/L or ≥50 x 10^9/L if bone marrow is >50% involved by plasma cells, no transfusions allowed to reach these numbers • Total bilirubin ≤1.5 × upper limit of normal (ULN) • Alanine aminotransferase ≤2.5 × ULN • Estimated glomerular filtration rate ≥30 mL/min/1.73 m^2, calculated using the Modified Diet in Renal Disease formula
Exclusion criteria
• Patients who were assigned a IMWG frailty score of 0 were deemed ineligible for this study due to potential eligibility for proceeding to high dose therapy and autologous stem cell transplantation
• Presence of another primary malignancy
• Uncontrolled active infection, including active hepatitis or HIV infection
• Severe heart failure
Additional information
All patients were assessed at baseline for frailty according to IMWG frailty index based on age, Activities of Daily Living (ADL) score, Instrumental Activities of Daily Living score and comorbidities (Charlson Comorbidity Index)[27]
Contraception is used throughout the study

Table S2 Adverse events included in the evaluation of dose-limiting toxicities

Hematological toxicities
• ≥ Grade 3 febrile neutropenia lasting more than 48h despite adequate treatment • Grade 4 thrombocytopenia with platelet count ≤25 $\times 10^9$/L accompanied by clinically significant bleeding
Non-hematological toxicities
• Any ≥Grade 3 toxicity which is more severe than expected for an individual agent, or which does not resolve with appropriate supportive treatment within 48h • Any ≥ Grade 3 non-hematologic laboratory value if the abnormality leads to hospitalization • Grade 4 corneal events • Any organ-specific toxicities, including liver toxicity meeting prespecified liver stopping criteria