Low-dose belantamab mafodotin (belamaf) in combination with nirogacestat vs belamaf monotherapy in patients with relapsed/refractory multiple myeloma (RRMM): Phase 1/2 DREAMM-5 platform sub-study 3

Poster No. P913

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Introduction

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

The DREAMM-2 trial (NCT0352678) evaluated belamaf in patients with RRMM, and on the basis of the primary analysis (overall response rate 31%)[4,5] belamaf was approved in Europe* for patients with MM who have received 4 or more prior therapies and are refractory to a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 mAb.[5,6]

Nirogacestat (niro, PF-03084014, SpringWorks Therapeutics) is an investigational oral, selective, small molecule gamma secretase inhibitor that prevents the cleavage of several transmembrane proteins.[7,8] Gamma secretase has been found to cleave membrane-bound BCMA (mBCMA), releasing the extracellular domain as soluble BCMA (sBCMA) into circulation,[9] which interferes with and limits efficacy of BCMA-directed therapies.[9]

Preclinical data demonstrate that niro may increase cell-surface levels of BCMA and reduce sBCMA levels, which could enhance anti-BCMA agent activity in MM.[9] Based on in vitro experiments and clinical pharmacokinetics (PK), a niro dose of 100 mg twice-daily (BID) is expected to sustainably reduce sBCMA and increase mBCMA on MM cells.[9]

Belamaf is being evaluated in combination with niro in the DREAMM-5 Phase I/II platform trial (NCT04126200).[10,11] The combined mechanism of action is shown in **Figure 1B**. Data from the primary analysis are presented here.

*Due to the outcome of the DREAMM-3 trial (NCT04162210), in November 2022 the marketing authorization in the US was withdrawn following the request of the US Food and Drug Administration.

Objective

To determine if low dose belamaf in combination with niro provides similar efficacy to single-agent belamaf with an improved ocular safety profile.

Figure 1. A. Belamaf Mechanisms of Action and B. Belamaf and Niro Combined Mechanism of Action

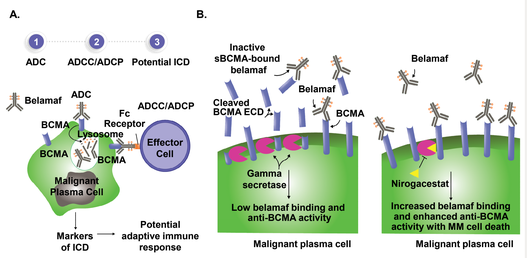
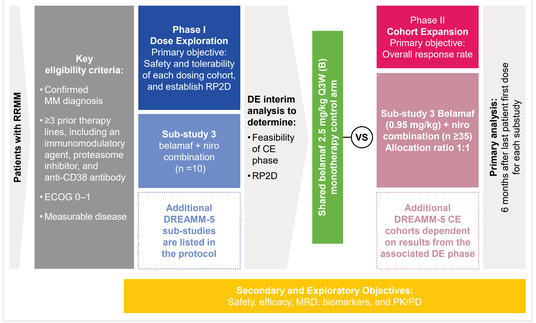


Figure A. from Nooka AK et al. *Future Oncol.* 2021;17:1987–2003.
Figure B from SpringWorks Therapeutics, with permission. © SpringWorks Therapeutics, all rights reserved.

Methods

Figure 2. DREAMM-5 Platform Study Design



The Phase 1/2 platform study incorporates a master protocol evaluating multiple belamaf-containing combinations in distinct sub-studies to identify efficacious combinations.[10,11]

Each sub-study begins with a dose-exploration (DE) phase; sub-studies demonstrating efficacy in a successful DE phase move into a subsequent cohort-expansion (CE) phase to compare the combination with a shared single-agent belamaf control arm.[10,11]

Adverse events (AE) were graded according to the National Cancer Institute Common Terminology for Adverse Events (CTCAE) version 5 (Grade [Gr] 1 mild–Gr 5 death related to AE).[12]

Eye examination findings and changes in best corrected visual acuity (BCVA) were graded by the CTCAE scale[12] until protocol amendment in June 2021 and thereafter KVA scale (Gr 1/mild–Gr 4/severe).[13] Therefore, ocular events are reported by CTCAE-5 for the DE cohort and KVA scale for the CE cohorts.

Primary outcome measures in the DE phase include dose-limiting toxicities, AE, and serious adverse events (SAE). Secondary outcome measures included overall response rate (ORR) according to International Myeloma Working Group (IMWG) Response Criteria.[14] The primary outcome in the CE phase was ORR, and secondary outcomes included clinical benefit rate, progression-free survival, duration of response, time to response, rates of partial response and better categories, and overall survival.

The DE phase of sub-study 3 evaluated low-dose belamaf 0.95 mg/kg every 3 weeks (Q3W) + niro 100 mg BID continuously (belamaf + niro combination) and included 10 patients in an initial cohort. Results of interim analysis of this sub-study DE arm led to opening of a randomised CE phase.

This poster presents data from patients randomised 1:1 to the belamaf 2.5 mg/kg Q3W monotherapy control arm (belamaf monotherapy; CE arm) or belamaf (0.95 mg/kg) + niro combination (CE arm; DE arm results also shown). In CE phase, dose reductions for toxicity mitigation were permitted for belamaf but not for niro.

The primary analysis for ORR in the CE phase compared the response rate in belamaf + niro combination therapy with belamaf monotherapy. In a pre-specified Bayesian analysis, data from DREAMM-2 [ORR 31% (30/97)][6] was used to construct a prior probability distribution for ORR in the belamaf monotherapy arm, and data from the DE phase were used for a prior probability distribution for the belamaf + niro combination arm. Each prior specified a range of plausible ORR values for the respective treatment arm, and how likely these were. The priors were then updated using the observed ORR in the corresponding CE phase arm to give a posterior probability distribution for ORR.

Results

Primary analysis results from the DE phase cohort (n=10) with low-dose belamaf (0.95 mg/kg) + niro (100 mg) combination, CE phase cohort (n=34) with belamaf (0.95 mg/kg) + niro (100 mg) combination, and CE phase cohort (n=37) with belamaf (2.5mg/kg) monotherapy cohort are presented.

Patient characteristics for the DE and CE cohorts are shown in **Table 1**. Cohorts were not balanced for high-risk cytogenetics and stage at screening; compared with the combination cohorts, the belamaf monotherapy CE cohort had approximately 50% fewer patients with extramedullary disease or stage III RRMM.

Table 1. Patient Characteristics

Characteristic, n (%)		Belamaf + Niro Combination DE, n=10	Belamaf + Niro Combination CE, n=34	Belamaf Monotherapy CE, n=37
Age, median (range), years		72.0 (56–86)	69.5 (48–79)	66.0 (56–81)
Sex	Male	5 (50)	16 (47)	21 (57)
	Female	5 (50)	18 (53)	16 (43)
ECOG-PS	0–1	10 (100)	34 (100)	36 (97)
High-risk cytogenetics		8 (80)	19 (56)	16 (43)
Stage at screening	I	1 (10)	14 (41)	14 (38)
	II	6 (60)	10 (29)	12 (32)
	III	3 (30)	10 (29)	6 (16)
	Unknown	0	0	5 (14)
Myeloma immunoglobulin	IgA	3 (30)	7 (21)	11 (30)
	IgD	0	0	2 (5)
	IgE	0	0	0
	IgG	6 (60)	20 (59)	19 (51)
	IgM	0	0	0
	None Present	1(10)	7 (21)	5 (14)
Myeloma light chain	Kappa Light Chain	7 (70)	22 (65)	23 (62)
	Lambda Light Chain	3 (30)	10 (29)	12 (32)
	No	0	2 (6)	2 (5)
Extramedullary disease	Yes	2 (20)	7 (21)	4 (11)
	No	8 (80)	25 (74)	32 (86)
	Unknown	0	2 (6)	1 (3)
Autologous stem cell transplant	Yes	9 (90)	25 (74)	24 (65)
	No	1 (10)	9 (26)	13 (35)
Prior lines of therapy, median (range)		4.5 (3–10)	5.0 (3–14)	5.0 (3–9)

Safety

In both DE and CE combination cohorts, all patients experienced AEs. A majority experienced ≥1 AE related to study treatment (**Table 2**).

In the DE belamaf + niro combination cohort, there were 2 fatal SAEs (intracranial haemorrhage, 1 patient; sepsis, 1 patient), neither of which were related to study treatment. In the CE belamaf + niro combination cohort, there were 2 fatal SAEs (sudden death and COVID-19 pneumonia) and in the belamaf monotherapy cohort there was 1 fatal SAE (COVID-19 infection); all were unrelated to study treatment.

Grade 3–4 AEs related to belamaf were consistent with the known safety profile of belamaf with low rates of drug-related Grade 3–4 eye disorders AEs across the cohorts. Niro Grade 3–4 AEs were primarily in the gastrointestinal and metabolism system organ class, as expected (**Table 3**).

Although the overall rate of ocular events was similar, there was a distinct shift to lower grades in the combination cohorts (**Table 4**). In the CE phase, Grade 3 ocular events were more common in the belamaf monotherapy cohort (59%) than in the belamaf + niro combination cohort (29%); there were no Grade 4 ocular events (**Table 4**).

Table 2. AE Summary

n (%)	Belamaf + Niro Combination DE, n=10	Belamaf + Niro Combination CE, n=34	Belamaf Monotherapy CE, n=37
Any AE	10 (100)	34 (100)	35 (95)
AEs related to study treatment	10 (100)	27 (79)	28 (76)
Grade 3–4 AEs	9 (90)	26 (76)	24 (65)
Grade 3–4 AEs related to belamaf	3 (30)	2 (6)	5 (14)
Grade 3–4 AEs related to niro	5 (50)	7 (21)	0
AE leading to dose interruption/delay	8 (80)	18 (53)	11 (30)
Dose interruptions related to belamaf	5 (50)	2 (6)	7 (19)
Dose interruptions related to niro	1 (1)	12 (35)	0
Dose interruptions related to both	3 (3)	0	0
AE leading to dose reduction	4 (40)	3 (9)	2 (5)
AE leading to permanent discontinuation of study treatment	2 (20)	3 (9)	0
Any SAE	7 (70)	14 (41)	12 (32)
SAEs related to study treatment	2 (20)	1 (3)	5 (14)
Fatal SAE	2 (20)	2 (6)	1 (3)
Fatal SAE related to study treatment	0	0	0

Table 3. Drug-related Grade 3–4 AEs by System Organ Class and Preferred Term

n (%)	Belamaf + Niro Combination DE, n=10	Belamaf + Niro Combination CE, n=34	Belamaf Monotherapy CE, n=37
Blood and Lymphatic	4 (40)	7 (21)	4 (11)
Thrombocytopenia	2 (20)	5 (15)	3 (8)
Anemia	1 (10)	2 (6)	0
Neutropenia	1 (10)	0	1 (3)
Febrile Neutropenia	0	0	1 (3)
Gastrointestinal	1 (10)	4 (12)	1 (3)
Diarrhoea	1 (10)	2 (6)	1 (3)
Abdominal pain upper	0	1 (3)	0
Nausea	0	1 (3)	0
Vomiting	0	1 (3)	0
Eye disorders	3 (30)	1 (3)	2 (5)
Vision blurred	0	1 (3)	0
Dry eye	0	0	1 (3)
Photophobia	0	0	1 (3)
Eye pain	1 (10)	0	0
Eye disorder	1 (10)	0	0
Visual impairment	1 (10)	0	0
Corneal epithelial microcysts	1 (10)	0	0
Keratitis	1 (10)	0	0
Punctate keratitis	1 (10)	0	0
Investigations	0	2 (6)	6 (16)
Blood bilirubin increase	0	1 (3)	0
AST increase	0	0	2 (5)
Platelet count decrease	0	1 (3)	3 (8)
Blood urea increase	0	0	0
Neutrophil count decrease	0	0	1 (3)
Transaminases increase	0	0	1 (3)
Vascular disorders	1 (10)	1 (3)	0
Hypertension	1 (10)	1 (3)	0
Metabolism and nutrition	1 (10)	5 (15)	0
Hypophosphataemia	1 (10)	4 (12)	0
Hyponatraemia	0	1 (3)	0
Injury, poisoning, and procedural complications	2 (20)	0	1 (3)
Infusion related reaction	2 (20)	0	1 (3)
Nervous system disorders	0	1 (3)	0
Peripheral sensory neuropathy	0	1 (3)	0
Musculoskeletal and connective tissue	0	0	1 (3)
Pathological fracture	0	0	1 (3)

Table 4. Summary of Ocular Events Based on CTCAE-5 and KVA Scales

	Belamaf + Niro Combination DE, n=10 CTCAE 5	Belamaf + Niro Combination CE, n=34 KVA scale	Belamaf Monotherapy CE, n=37 KVA scale
Subjects with any ocular event, n (%)	5 (50)	24 (71)	29 (78)
Grade 1	1 (10)	7 (21)	2 (5)
Grade 2	2 (20)	7 (21)	5 (14)
Grade 3	2 (20)	10 (29)	22 (59)
Grade 4	0	0	0

Efficacy

Median (range) number of cycles received were: belamaf + niro combination DE cohort 9.5 (1–31), belamaf + niro combination CE cohort 4.0 (1–20) and belamaf monotherapy CE cohort 3.0 (1–9) (**Table 5**).

Median (range) follow-up duration (weeks) was: belamaf + niro combination DE cohort 51 (5–106), belamaf + niro combination CE cohort 29.5 (1–57) and belamaf monotherapy CE cohort 27.0 (1–56).

Table 5. Summary of Belamaf Exposure (CE Phase)

	Belamaf + Niro Combination DE, n=10	Belamaf + Niro Combination CE, n=34	Belamaf Monotherapy CE, n=37
Number of Cycles, median (range)	10 (1–31)	4 (1–20)	3 (1–9)
Dose Intensity, median (range), mg/kg/3 wk	0.90 (0.44–0.95)	0.94 (0.29–0.97)	1.46 (0.44–2.54)

Table 6. Overall Response Rate by Cohort

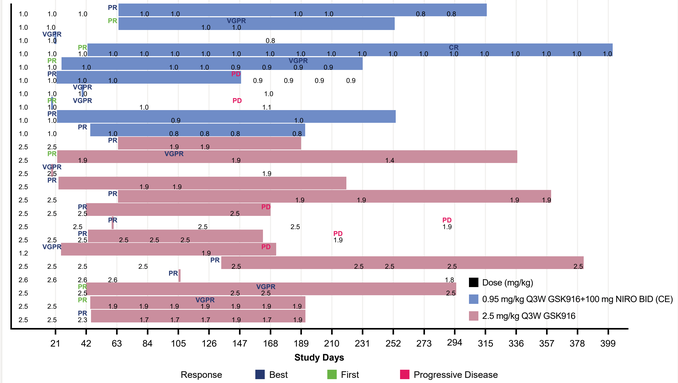
Response by cohort	Belamaf + Niro Combination DE, n=10	Belamaf + Niro Combination CE, n=34	Belamaf Monotherapy CE, n=37
Best Response, n (%)			
sCR	0	0	0
CR	0	1 (3)	0
VGPR	3 (30)	5 (15)	5 (14)
PR	3 (30)	4 (12)	9 (24)
MR	0	2 (6)	4 (11)
SD	1 (10)	12 (35)	11 (30)
PD	3 (30)	5 (15)	6 (16)
NE	0	5 (15)	2 (5)
ORR, n (%) [95% CI]	6 (60) [26.2, 87.8]	10 (29) [15.1, 47.5]	14 (38) [22.5, 55.2]
***Posterior probability ORR, median (95% credible interval), %**	-	36 (21, 51)	33 (25, 47)
Clinical benefit rate, n (%) [95% CI]	6 (60) [26.2, 87.8]	12 (35) [19.7, 53.5]	18 (49) [31.9, 65.6]

*Incorporating prior ORR for low-dose belamaf + niro from DREAMM-5 sub-study 3 DE cohort (observed ORR 60% [6/10]) and for monotherapy from DREAMM-2 2.5mg/kg monotherapy cohort (observed ORR 31% [30/97]) per prespecified analysis plan.

For the CE phase combination and monotherapy cohorts, respectively, observed ORR was 29% (95% CI 15.1, 47.5) and 38% (22.5, 55.2) (**Table 6**). This resulted in median ORR values of 36% (95% credible interval: 21%, 51%) and 33% (25%, 47%), respectively, from the posterior probability distribution. For the CE phase combination and monotherapy cohorts, respectively, 3% and 0% achieved complete response (CR), and 15% and 14% achieved very good partial response (VGPR).

Median duration of response (95% CI) in the belamaf + niro combination DE subjects was not reached (NR) (5.6–NR) months. For the CE phase combination and monotherapy cohorts, respectively, median duration of response (95% CI) was NR (4.2–NR) months and NR (4.1–NR) (**Figure 3**).

Figure 3. Profile of Responders in CE Phase (Combination Cohort)



*Numbers indicate the dose received (mg/kg) and timing of dose.

Conclusions

While single-agent belamaf continues to demonstrate strong efficacy, low-dose belamaf + niro demonstrated an encouraging ORR with a substantial reduction of high-grade ocular events, consistent with the hypothesis that niro increases BCMA target density.

The AE profile seen with the belamaf + niro combination appears consistent with the known safety profiles of each agent.

These data support ongoing exploration in DREAMM-5 of belamaf + niro + standard of care agents in patients with RRMM.

Disclosures

NSC, **KK**, **JHL**, **TF**, **JCJ**, and **SG** have no disclosures to report; **PGR** has received consultancy fees from Celgene, Janssen, Takeda, Karyopharm Therapeutics, Oncopeptides, Sanofi, Jazz Pharmaceuticals, and Secura Bio; research funding from Celgene, Takeda, Bristol-Myers Squibb, Oncopeptides; **MH** has received donoraria from Janssen, BMS, Novartis; research funding from GSK, Lilly, Janssen; **VR** has received honoraria from AZD, Infinity Pharmaceuticals, Gilead Sciences, NanoString Technologies, Roche, Novartis, AbbVie; consultancy fees from Infinity Pharmaceuticals, PharaMar, Gilead Sciences, NanoString Technologies, BMS, MSD, Roche/Genentech, Immune Design, Roche, and Incyte; research funding from arGEN-XBVBA, Epizyme, Astex Pharmaceuticals, GSK/Adaptimmune; paid expert testimony for SERVIER; travel expenses from Roche, BMS, AZD; **JML** has received consultancy fees from BMS, Janssen, Novartis, Sanofi, GSK, Gilead; research funding from BMS, Janssen; received fees from speakers' bureau participation for BMS, Janssen, Novartis, Sanofi, GSK, Gilead; **MD** received fees from speakers' bureau participation for Amgen, BeiGene, BMS, Janssen, Takeda; **FS** has received honoraria from Amgen, BMS, Takeda, AbbVie, Janssen, Novartis, SkyliteDX, Oncopeptides, Sanofi, Pfizer, Daiki-Sankyo, GSK; consultancy fees from AbbVie, GSK, Celgene, Takeda, Janssen, Oncopeptides, Sanofi, BMS; research funding from Celgene, Janssen, Oncopeptides, Sanofi, GSK, Targovax; **CKM** has received honoraria from Takeda, Amgen, Celgene, and Janssen Cilag; **MM** has received honoraria from Accord, BMS, Janssen, Sandoz, Novartis, Amgen; research funding from GSK, Janssen, Lilly, Sanofi, Oncopeptides, Astra Zeneca, AbbVie; **SC**, **LMS**, and **CJB** are employees of and hold stocks and share in SpringWorks Therapeutics; **CB**, **HS** and **JLM** are employees of and hold stocks and share in GSK.

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