Synergistic Effects of Low-dose Belantamab Mafodotin in Combination with a Gamma-Secretase Inhibitor (Nirogacestat) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM): DREAMM-5 Study

Poster No. 443

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Background

- Belantamab mafodotin (belamaf), a B-cell maturation antigen (BCMA)-targeting antibody-drug conjugate has a multimodal mechanism of action that eliminates multiple myeloma (MM) cells via direct cytotoxicity as well as by a systemic anti-MM tumor immune response.[1-3] (**Figure 1A**)
- Belamaf 2.5 mg/kg Q3W is the only BCMA-targeted ADC monotherapy approved for the treatment of patients with triple class refractory/exposed MM.[4,5]
- Belamaf is currently approved as a single agent (2.5 mg/kg Q3W) in patients with RRMM with a 31% overall response rate (ORR) and 46.3% Gr3/4 keratopathy based on the keratopathy visual acuity (KVA) scale.[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 PK, a niro dose of 100 mg BID is expected to sustainably reduce sBMCA and increase mBCMA on MM cells.[9]
- Belamaf is being evaluated in the DREAMM-5 Phase I/II platform trial in combination with niro (NCT04126200).[10,11] The combined mechanism of action is shown in **Figure 1B.**

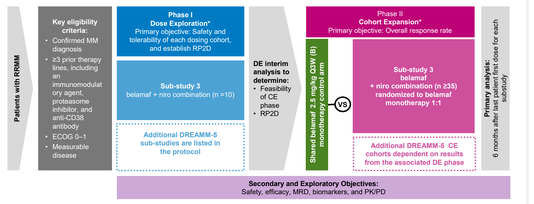
Objective

To determine if belamaf in combination with niro results in similar efficacy compared to single agent belamaf and an improved ocular safety profile

Methods

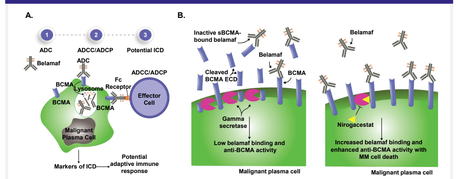
- The trial design for the DREAMM-5 platform trial is shown in **Figure 2.**
- The Phase 1/2 platform study incorporates a master protocol evaluating multiple belamaf-containing combinations in distinct sub-studies to identify efficacious combinations.[10,11]
- Each sub-study begins with a dose-exploration (DE) arm; sub-studies that demonstrate efficacy in a successful DE phase will move into a subsequent cohort-expansion (CE) arm 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–Gr5 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 (Gr1/mild–Gr4/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 arm include dose limiting toxicities, AE, and serious adverse events (SAE). Secondary outcome measures included ORR according to International Myeloma Working Group (IMWG) Response Criteria.[14]
- The DE arm of sub-study 3 evaluated low-dose belamaf 0.95 mg/kg Q3W + niro 100 mg BID continuously **(belamaf + niro combination)** and included 10 patients in this cohort. Results of interim analysis of this substudy DE arm led to opening of randomized CE arm.
- This poster presents preliminary data from the planned interim analysis of 28 patients (70 patients planned total) from cohort expansion randomized 1:1 to belamaf 2.5mg/kg monotherapy control arm **(belamaf monotherapy)** or belamaf + niro combination based on results from DE of the belamaf + niro combination.
- The primary analysis for ORR will be based on the Bayesian approach[15] and will be used to compare the response rate in belamaf + niro combination therapy with belamaf monotherapy. In the Bayesian analysis, the data from DREAMM-2 [ORR 31% (30/97)][6] was used as informative prior for the belamaf monotherapy arm, and the data from the DE phase was used as informative prior for the belamaf + niro combination therapy.
- The planned interim analysis for futility included 28 CE patients randomized 1:1 into two cohorts belamaf + niro combination vs belamaf monotherapy. The futility criterion is the posterior probability of response rate in combination being greater than the response rate in monotherapy is less than 40%.

Figure 2. DREAMM-5 Platform Study Design



*Dose modifications for belamaf 2.5 mg/kg monotherapy were allowed however, for belamaf 0.95 mg/kg Q3W dose modifications were not permitted per study protocol
Belamaf, belantamab mafodotin; CD38, cluster of differentiation-38; CE, cohort expansion; DE, dose exploration; ECOG, Eastern Cooperative Oncology Group Performance Score; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; niro, nirogacestat; ORR, overall response rate; PD, pharmacodynamics; PK, pharmacokinetics; RP2D, recommended phase II dose.

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



ADC, antibody-drug conjugate; ADCC/P, antibody-dependent cellular cytotoxicity/phagocytosis; APP, amyloid precursor protein; BCMA, B-cell maturation antigen; DREAMM, DRiving Excellence in Approaches to Multiple Myeloma; ECD, extracellular domain; GSI, gamma secretase inhibitor; ICD, immunogenic cell death; MM, multiple myeloma; sBCMA, soluble BCMA, RRMM, relapsed/refractory multiple myeloma. Figure A, from Nooka AK et al. *Future Oncol.* 2021;17:1987-2003. Figure B from Springworks Therapeutics, with permission.
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Results

Results from the DE arm cohort (n=10) with belamaf + niro combination, as well as the planned interim analysis results from the two CE arm cohorts (n=28 with at least 3 post-baseline assessments) comparing the belamaf + niro combination therapy (same dose as DE arm cohort) vs belamaf monotherapy are presented.

Patient Characteristics

- Patient characteristics for the DE and CE cohort arms are shown in **Table 1.**

Table 1. Patient Characteristics

Characteristic		Belamaf + Niro Combination DE n=10	Belamaf + Niro Combination CE n=14	Belamaf Monotherapy CE n=14
Age, years, median (range)		72.0 (56–86)	70.5 (55-77)	65.5 (56-80)
Sex, n (%)	**Male**	5 (50)	7 (50)	5 (36)
	Female	5 (50)	7 (50)	9 (64)
ECOG-PS	**0–1**	10 (100)	14 (100)	14 (100)
High-risk cytogenetics		8 (80)	7 (50)	6 (43)
Stage at screening	**I**	1 (10)	4 (29)	4 (29)
	II	6 (60)	5 (36)	5 (36)
	III	3 (30)	5 (36)	2 (14)
	Unknown	0	0	3 (21)
Myeloma Immunoglobulin	**IgA**	3 (30)	2 (14)	4 (29)
	IgD	0	0	1 (7)
	IgE	0	0	0
	IgG	6 (60)	10 (71)	8 (57)
	IgM	0	0	0
	None Present	1(10)	2 (14)	1 (7)
Myeloma light chain	**Kappa Light Chain**	7(70)	9 (64)	8 (57)
	Lamda Light Chain	3(30)	5 (36)	5 (36)
	No	0	0	1 (7)
Extramedullary disease	**Yes**	2(20)	4 (29)	1 (7)
	No	8 (80)	10 (71)	13 (93)
Autologous stem cell transplant	**Yes**	9 (90)	10 (71)	9 (64)
	No	1 (10)	4 (29)	5 (36)
Prior lines of therapy, median (min–max)		4.5 (3–10)	4.5 (3–10)	4.5 (3–7)

Belamaf, belantamab mafodotin; CE, cohort expansion; DE, dose exploration; ECOG-PS, Eastern Cooperative Oncology Group Performance Score; Ig, Immunoglobulin; Niro, nirogacestat

Safety

- In both DE arm and CE arm cohorts, all patients experienced an AE; most were considered related to study treatment (**Table 2.**
- Grade ≥3 AEs related to belamaf occurred at different rates across cohorts, with the lower rates in both the belamaf + niro combination DE and CE cohorts.
- In the DE belamaf + niro combination cohort, there were 2 fatal SAEs (intracranial hemorrhage, 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 (hematuria and COVID-19 infection) and in the belamaf monotherapy cohort there was 1 fatal SAE (COVID-19 infection) all which were unrelated to study treatment.

Table 2. AE Summary

n (%)	Belamaf + Niro Combination DE n=10	Belamaf + Niro Combination CE n=14	Belamaf Monotherapy CE n=14
Any AE	10 (100)	14 (100)	14 (100)
AEs related to study treatment	10 (100)	12 (86)	12 (86)
Grade ≥3 AEs	9 (90)	11 (79)	10 (71)
Grade ≥3 AEs related to belamaf	3 (30)	1 (7)	5 (36)
AE leading to dose interruption/delay	8 (80)	10 (71)	8 (57)
AE leading to dose reduction	4 (40)	3 (21)	2 (14)
Dose reductions related to belamaf*	-	-	2(14)
Dose reductions related to niro	4 (40)	2(14)	-
Dose reductions related to both	-	1 (7)	-
AE leading to permanent discontinuation of study treatment	2(20)	1 (7)	0
Any SAE	5 (50)	5 (36)	4 (29)
SAEs related to study treatment	3 (30)	0	1 (7)
Fatal SAE	2 (20)	2 (14)	1 (7)
Fatal SAE related to study treatment	0	0	0

*Dose reductions from the 0.95 mg/kg belamaf starting dose were not permitted
AE, adverse event; Belamaf, belantamab mafodotin; CE, cohort expansion; DE, dose exploration; SAE, serious adverse event; Niro, nirogacestat.

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

	Belamaf + Niro Combination DE n=10	Belamaf + Niro Combination CE n=14	Belamaf Monotherapy CE n=14
	Grade ≥3	Grade ≥3	Grade ≥3
Blood and Lymphatic	3 (30)	4 (29)	2 (14)
Thrombocytopenia	2 (20)	3 (21)	2 (14)
Febrile neutropenia	1 (10)	1 (7)	1 (7)
Gastrointestinal	1 (10)	3 (21)	1 (7)
Diarrhea	1 (10)	2 (14)	1 (7)
Abdominal pain Upper	-	1 (7)	-
Investigations	0	2 (14)	3 (21)
Blood magnesium decrease	-	-	-
AST increase	-	-	1 (7)
Platelet count decrease	-	1 (7)	2 (14)
Blood urea increase	-	1 (7)	-
General and administration site conditions	0	0	0
Metabolism and nutrition	1 (10)	1 (7)	0
Hypophosphatemia	1 (10)	1 (7)	
Injury and procedural complications	2 (20)	0	1 (7)
IRR	2 (20)		1 (7)
Renal and urinary	0	1 (7)	0
Proteinuria	-	1 (7)	
Respiratory, thoracic and mediastinal	-	0	1 (7)
Pulmonary embolism			1 (7)
Musculoskeletal and connective tissue	-	0	0

AE, adverse event; AST, aspartate aminotransferase; Belamaf, belantamab mafodotin; CE, cohort expansion; DE, dose exploration; Gr, grade; IRR, infusion related reaction; SAE, serious adverse event; Niro, nirogacestat.

- A summary of ocular events are based on CTCAE-5 (DE cohort) and KVA (CE cohort) (**Table 4.**
- Grade ≥3 ocular events in the belamaf + niro combination DE cohort were present in 20% of the cohort.
- In CE cohorts Grade ≥3 ocular events were more common in the belamaf monotherapy cohort (50%) than in the belamaf + niro combination (7%).

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

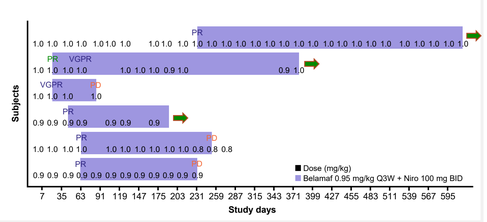
Response by Cohort	Belamaf + Niro Combination DE n=10	Belamaf + Niro Combination CE n=14	Belamaf Monotherapy CE n=14
	CTCAE 5	KVA scale	KVA Scale
Subjects with any Ocular Event, n (%)	6 (60)	7 (50)	12 (86)
Grade 1	2 (20)	4 (29)	0
Grade 2	2 (20)	2 (14)	5 (36)
Grade 3	2 (20)	1 (7)	7 (50)
Grade 4	0	0	0

Belamaf, belantamab mafodotin; CE, cohort expansion; CTCAE, Common Terminology for Adverse Events; DE, dose exploration; KVA, keratopathy and visual acuity; Niro, nirogacestat.

Efficacy

- Median (range) number of cycles received were; belamaf + niro combination DE cohort 8.5 (1–29), belamaf + niro combination CE cohort 4.0 (1–9) and belamaf monotherapy CE cohort 2.0 (1–5).
- Median (range) follow-up duration (weeks) was; belamaf + niro combination DE cohort 34.5 (5–88), belamaf + niro combination CE cohort 12.0 (3–24) and belamaf monotherapy CE cohort 12.0 (3–22).
- Median duration of response (CI) in the belamaf + niro combination DE subjects was 6.2 (2.1–NR) months (**Figure 3A**). Data are not mature enough to calculate duration of response for the CE cohorts, and therefore not included.
- The results of this interim evaluation did not meet the futility stopping criteria.
- ORR for belamaf + niro combination DE and CE cohorts combined was 38% with 17% achieving VGPR (**Table 5**).
- The estimated ORRs and 95% credible interval were 36% (25%-69%) in the belamaf monotherapy and 35% (12%-56%) in the belamaf + niro combination when borrowing data from DREAMM 2 and the belamaf + niro combination DE phase.

Figure 3A: Profile of Responders in Belamaf + Niro Combination DE Phase



Belamaf, belantamab mafodotin; BID, twice daily; CE, cohort expansion; CI, confidence interval; CR, complete response; DE, dose exploration; NE, not evaluable; Niro, nirogacestat; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Figure 3B: Profile of Responders in CE Phase.

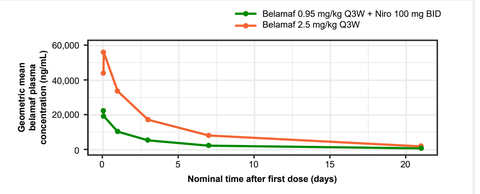
Data are not mature enough to calculate duration of response for belamaf + niro combination CE subjects

Table 5. Overall Response Rate by Cohort

Response by Cohort	Belamaf + Niro Combination DE n=10	Belamaf + Niro Combination CE n=14	Belamaf + Niro Combination CE + DE n=24	Belamaf Monotherapy CE n=14
Best Response, n (%)				
sCR	0	0	0	0
CR	0	0	0	0
VGPR	2 (20)	2 (14)	4 (17)	0
PR	4 (40)	1 (7)	5 (21)	7 (50)
MR	0	0	0	1 (7)
SD	1 (10)	8 (57)	9 (38)	4 (29)
PD	3 (30)	1 (7)	4 (17)	0
NE	0	2 (14)	2 (8)	2 (14)
ORR, n (%) [95% CI]	**6 (60)** [26.2, 87.8]	**3 (21)** [4.7, 50.8]	**9 (38)** [18.8, 59.4]	**7 (50)** [23.0, 77.0]
Clinical benefit, n (%) [95% CI]	6 (60) [26.2, 87.8]	3 (21) [4.7, 50.8]	9 (38) [18.8, 59.4]	8 (57) [28.9, 82.3]

Belamaf, belantamab mafodotin; BID, twice a day; CE, cohort expansion; CI, confidence interval; CR, complete response; DE, dose exploration; MRD, minimal response; NA, not applicable; NE, not evaluable; Niro, nirogacestat; ORR, overall response rate; PD, progressive disease; PR, partial response; Q3W, every three weeks; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Figure 4. Belamaf Plasma Concentrations for CE Cohorts Over Time After Dose for Cycle



Belamaf, belantamab mafodotin; CE, cohort expansion; CI, confidence interval; CR, complete response; DE, dose exploration; NE, not evaluable; Niro, nirogacestat; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Belamaf Pharmacokinetic Data

- Preliminary belamaf (ADC) pharmacokinetic data for the belamaf + niro combination and belamaf monotherapy CE cohorts are presented in **Figure 4.**
- Belamaf PK profiles were similar to that previously observed in patients with RRMM.[16,17]
- Proportionally lower exposures at 0.95 mg/kg belamaf are consistent with the lower incidence of ocular events in the combination compared to the belamaf monotherapy arm.[13]

Conclusions

- This preliminary data suggests a manageable safety profile with low-dose belamaf (0.95 mg/kg Q3W) + nirogacestat (100 mg BID continuously) combination in patients with heavily pretreated RRMM.
- Reduced ocular events, particularly Grade ≥3, 12.5% (2/10 in DE and 1/14 in CE) were observed in patients dosed with low dose belamaf + nirogacestat.
- The ORR in belamaf + nirogacestat combination cohorts was 38% (9/24) and 17% achieved VGPR (4/24).
- New sub-studies will evaluate belamaf + nirogacestat with standard of care treatments (Rd, Pd) as a quadruplet regimen to improve efficacy and reduce ocular events in patients with RRMM.[11]

Abbreviations

AE, adverse event; BCMA, B-cell maturation antigen; belamaf, belantamab mafodotin; BID, twice daily; CD38, cluster of differentiation-38; CE, cohort expansion; CYP3A4, cytochrome P450 3A4; DE, dose exploration; ECOG-PS, Eastern Cooperative Oncology Performance Score; Gr, grade; IMWG, International Myeloma Working Group; MM, multiple myeloma; Niro, nirogacestat; ORR, overall response rate; Q3W, every 3 weeks, PD, pharmacodynamics; Pd, Pomalidomide + dexamethasone; PK, pharmacokinetics; Rd, Lenalidomide + dexamethosone; RP2D, recommended Phase II dose; RRMM, relapsed/refractory multiple myeloma; SAE, serious adverse event; sBCMA, soluble BCMA.

Disclosures

SG, **MH**, **TF** and **KU** have no interests to declare. **SL** has received research funding from Celgene and Takeda, and honoraria from Novartis, BMS, GSK, Amgen, Merck, and Janssen. **KS** has received consultancy fees from Janssen, BMS/Celgene, Amgen, Sanofi; honoraria from Janssen, BMS, Amgen, Sanofi. **NSC** has received research funding from Cellectar. **VR** has received consultancy fees from Infinity Pharmaceuticals, PharaMar, Gilead Sciences, NanoString Technologies, BMS, MSD, Roche/Genentech, Immune Design, Roche and Incyte; research finding from arGEN-X BVBA, Epizyme, Astex Pharmaceuticals, GlaxoSmithKline/Adaptimmune; honoraria from AZD, Infinity Pharmaceuticals, Gilead Sciences, NanoString Technologies, Roche, Novartis, AbbVie; paid expert testimony from SERVIER; and travel expenses from Roche, BMS, AZD. **HQ** has received consultancy fees from GlaxoSmithKline, Celgene, Karyopharm Therapeutics, Janssen-Cilag, CSL Behring, Amgen, Sanofi and Antengene; research funding from Celgene, Amgen, Karyopharm, GlaxoSmithKline and Sanofi. **VV** has received consultancy fees from AstraZeneca, Janssen Oncology, Sanofi, Novartis, BeiGene, Roche, AbbVie, Takeda, Gilead Sciences; and speakers bureau fees from AbbVie, AstraZeneca, Amgen, BioCad, Janssen, Sanofi, Novartis. **C-KM** has received honoraria from Takeda, Amgen, Celgene, and Janssen Cilag. **SC** is an employee of, and holds stocks and shares in, Springworks Therapeutics Springworks Therapeutics and was an employee of Janssen. **LMS** is an employee of and hold stocks and shares in Springworks Therapeutics. **JY**, **BEK** and **IG** are employees of and hold stocks and shares in GSK. **TC** is an employee of GSK. **BH** is an employee of and hold stocks and shares in GSK and has received patents or royalties from GSK. **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. **MCM** has received consultancy fees from Janssen-Cilag; and has received speakers bureau fees from Celgene/Bristol-Myers Squibb, Medscape, Janssen Medical Affair.

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