DREAMM-5 Platform Trial: Belantamab Mafodotin (Belamaf) in Combination with Four Different Novel Agents in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

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Background

Unmet need
Patients with heavily pre-treated RRMM have a poor prognosis; novel, well-tolerated treatments that induce lasting responses are warranted1,2

Belantamab mafodotin (belamaf; BLENREP)
- First-in-class anti-BCMA antibody-drug conjugate with multimodal mechanism of action2 (Figure)
- In the DREAMM-2 study, single-agent belamaf demonstrated a manageable safety profile and deep and durable clinical responses in patients with heavily pretreated RRMM with up to 13 months of follow-up4,5

Combination strategies
Combining belamaf with agents with complementary modes of action may increased efficacy or duration of response to address the unmet need in RRMM

Platform trial
The Platform trial is an efficient design incorporating a single master protocol, where multiple treatment combinations will be evaluated in separate sub-studies5,6


Methods: Platform Study Design

The DREAMM-5 platform trial (NCT04126200) is a Phase 1/2 study that incorporates an efficient design into one master protocol, wherein multiple belanaf-containing combinations will be evaluated in separate sub-studies to identify efficacious doublet combinations, vs a shared belanaf monotherapy control arm.

Key eligibility criteria:
- Confirmed MM diagnosis
- ≥3 prior therapy lines, including an immunomodulatory agent, proteasome inhibitor, and anti-CD38 antibody
- ECOG 0–2
- Measurable disease

### Phase 1
**Dose Exploration (DE)**

**Primary objective:** DLTs, AEs

- Sub-study 1: belanaf + anti-OX40 GSK3174998 (n ≤10 per dose level)
- Sub-study 2: belanaf + feladilimab (n ≤10 per dose level)
- Sub-study 3: belanaf + nirogacestat (n ≤10 per dose level)
- Sub-study 4: belanaf + dostarlimab (n ≤10 per dose level)

**DE interim analysis to determine:**
- Feasibility of CE phase
- RP2D

### Phase 2
**Cohort Expansion (CE)**

**Primary objective:** Overall response rate

- Sub-study 1: belanaf + anti-OX40 GSK3174998 (n ≥35)
- Sub-study 2: belanaf + feladilimab (n ≥35)
- Sub-study 3: belanaf + nirogacestat (n ≥35)
- Sub-study 4: belanaf + dostarlimab (n ≥35)

**More sub-studies can be added**

*sub-studies may include dose-escalation or de-escalation cohort(s) guided by modified toxicity probability interval principles; †Assignment to sub-study in DE will be according to treatment slot availability. When more than one sub-study or dose level is enrolling, allocation will be by pre-determined algorithm; ‡Participants in CE are stratified by sub-study and prior lines of therapy (3–4 vs >4); ‡Prior anti-BCMA therapy is permitted; **As measured by serum and/or urine M-protein and/or serum free light chain levels.

AE, adverse event; CE, cohort expansion; DE, dose explorations; DLT, dose-limiting toxicities; DREAMM, Driving Excellence in Approaches to Multiple Myeloma; ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; PD, pharmacodynamics; PK, pharmacokinetics; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma.
Sub-study 1: Belamaf + Anti-OX40 GSK3174998

**GSK3174998** is a humanized wild-type IgG1 anti-OX40 agonistic mAb that binds to the co-stimulatory OX40 receptor, expressed primarily on activated CD4+ and CD8+ T cells.

- OX40 signalling promotes effector T-cell proliferation and survival, while blocking the suppressive function of Treg cells.
- This induces a T-cell mediated immune response against cancer cells (Figure).
- GSK3174998 has potential to overcome immune resistance and enhance immune-mediated anti-cancer activity.
  - Pre-clinical data for belamaf plus a mouse OX40 surrogate antibody support the potential utility of combination therapy with belamaf and GSK3174998.

Combining belamaf with OX40 could increase anti-tumor activity via increased infiltration and activation of intra-tumor DCs, antigen-presenting T cells, and induce hallmarks of ICD potentially leading to an adaptive immune response.

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**APC, antigen-presenting cell; DC, dendritic cells; ICD, immunogenic cell death; IgG, immunoglobulin G; mAb, monoclonal antibody; Treg, regulatory T cell.**

Sub-study 2: Belamaf + Feladilimab

Feladilimab (GSK3359609) is a humanized anti-ICOS IgG4 mAb selected for its nanomolar binding to, and agonist activity in, ICOS-expressing CD4+ and CD8+ effector T cells.

ICOS is a co-stimulatory receptor member of the CD28 superfamily that plays an important role in the proliferation, differentiation, survival, and function of T cells.

Feladilimab was designed and Fc-optimised to enhance T-cell function and enable anti-cancer responses without the depletion of ICOS-expressing cells (Figure).

Combining belamaf with anti-tumor immune response-enhancing agents, such as feladilimab, could offer enhanced anti-tumor activity due to complementary mechanisms of action.

APC, antigen-presenting cell; CTLA4, cytotoxic T-lymphocyte-associated protein 4; CXCR5, C-X-C motif chemokine receptor 5; ICOS, inducible T-cell co-stimulatory; ICOS-L, ICOS ligand; IFN, interferon; IgG, immunoglobulin G; mAb, monoclonal antibody; MHC, major histocompatibility complex; TCR, T-cell receptor.

Sub-study 3: Belamaf + Nirogacestat

**Nirogacestat (PF-03084014, SpringWorks Therapeutics) gamma-secretase inhibitor**
that prevents the cleavage of transmembrane proteins including Notch, APP, and BCMA

Gamma secretase has been found to cleave membrane-bound BCMA, releasing the extracellular domain as sBCMA into circulation, which interferes with and limits efficacy of BCMA-directed therapies

Inhibition of gamma secretase activity has been shown to increase cell-surface levels and availability of BCMA and reduce sBCMA in circulation (Figure)

Pre-clinical data have shown synergistic effects of combining belamaf and nirogacestat, providing the rationale to support clinical evaluation of this combination in RRMM

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**Belamaf + Nirogacestat Combined Mechanism of Action**

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ADC, antibody-drug conjugate; APP, amyloid precursor protein; BCMA, B-cell maturation antigen; ECD, extracellular domain; GSI, gamma secretase inhibitor; MM, multiple myeloma; sBCMA, soluble BCMA.


American Society of Hematology
Sub-study 4: Belamaf + Dostarlimab

Dostarlimab is a humanized anti-PD-1 IgG4 mAb that blocks interactions between PD-1 and PD-L1 or PD-L2

Cancer cells have been shown to hijack the PD-1 checkpoint blockade by upregulating PD-L1 expression to evade immune control and facilitate tumor progression. Binding of PD-L1 or PD-L2 to PD-1 inhibits lymphocyte activation, blocking the immune-mediated anti-cancer response (Figure).

Early clinical data with dostarlimab showed encouraging anti-tumor activity in patients with endometrial cancer.

Expression of PD-1 and its ligands has been demonstrated in MM.

The addition of a PD-1 inhibitor to belamaf treatment has the potential to augment the anti-cancer response caused by belamaf-mediated ICD.

ICD, immunogenic cell death; IgG, immunoglobulin G; MM, multiple myeloma; PD-1, programmed cell death protein 1; PD-L1/2, programmed death-ligand 1 or 2.

Study Status

All sub-studies are at different stages of accrual

Additional sub-studies may be explored based on scientific rationale and/or pre-clinical combination study results

Belamaf is being evaluated in other combination strategies in various MM settings (posters 1419, 3247, 2302 at this meeting)
Further analyses of the pivotal DREAMM-2 study of single-agent belamaf are presented at this meeting (posters 1417, 2278, 3221, 3224, 3248)
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Sub-studies 1, 2, and 3 have been previously presented\(^1,2\)

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