DREAMM-5: Platform Trial Evaluating Belantamab Mafodotin (a BCMA-Directed Immunoconjugate) in Combination With Novel Agents in Relapsed/Refractory Multiple Myeloma (RRMM)

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Co-authors: PR has received grant funding and personal fees from Celgene, Takeda, and Oncopeptides; grant funding from Bristol-Myers Squibb (BMS), and personal fees from Janssen, Karyopharm, Amgen, and Sanofi. BH, NJ, TN, MB, SP, GF-B, AY, CS, RMO, CMA, MB, and EMP are employees of and hold stocks and shares in GlaxoSmithKline. LMS is an employee of and holds stocks and shares in SpringWorks.
Background

Unmet need

- Patients with RRMM who have relapsed through multiple prior lines of therapy need novel, effective, targeted agents

Belantamab mafodotin (belamaf; GSK2857916)

- First-in-class anti-BCMA antibody-drug conjugate with multimodal mechanisms of action (Figure)

- In the DREAMM-2 study, which is presented at this congress, single-agent belamaf demonstrated a manageable safety profile and rapid, deep and durable clinical responses in patients with heavily pretreated RRMM

Combination strategies

- Combining belamaf with agents with other mechanisms of action has the potential to achieve synergistic effects in multiple myeloma

- DREAMM-5 (NCT04126200) is a phase 1/2 platform trial in which multiple belamaf-containing combinations will be evaluated in sub-studies under one master protocol

Belaf Mechanisms of Action

1. ADC mechanism
2. ADCC/ADCP mechanism
3. Potential immunogenic cell death

ADC, antibody-drug conjugate; ADCC/ADCP, antibody-dependent cellular cytotoxicity/phagocytosis; BCMA, B-cell maturation antigen; DREAMM, DRiving Excellence in Approaches to Multiple Myeloma; RRMM, relapsed/refractory multiple myeloma.


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

**Dose exploration (Phase 1)**

- Each sub-study will consist of multiple dosing cohorts, and may involve dose-escalation or de-escalation cohorts.

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Sub-study</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10 per dose level</td>
<td>Sub-study 1</td>
</tr>
<tr>
<td>Belamaf GSK3174998</td>
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<tr>
<td>≤10 per dose level</td>
<td>Sub-study 2</td>
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<tr>
<td>Belamaf GSK3359609</td>
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<tr>
<td>≤10 per dose level</td>
<td>Sub-study 3</td>
</tr>
<tr>
<td>Belamaf Nirogacestat</td>
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<tr>
<td>≤10 per dose level</td>
<td>Sub-study 4</td>
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<tr>
<td>Belamaf D</td>
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More sub-studies can be added.

**Cohort expansion (Phase 2)**

- Patients will be randomised first to a sub-study then within a sub-study to either investigational combination treatment or shared belamaf monotherapy control arm.

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</table>

**Interim analysis based on ORR to determine**

1. Whether to proceed to cohort expansion
2. RP2D

**Primary analysis**

6 months after last patient first dose for each sub-study.

ORR, overall response rate; RP2D, recommended phase 2 dose.
## Objectives and Endpoints

<table>
<thead>
<tr>
<th>Dose escalation</th>
<th>Primary</th>
<th>Endpoints</th>
<th>Secondary</th>
<th>Objectives</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>Assess safety and tolerability of belamaf in combination with other anti-cancer treatments and establish recommended phase 2 dose</td>
<td>Dose-limiting toxicities* AEs</td>
<td>Objective</td>
<td>Evaluate clinical efficacy measures</td>
<td>Overall response rate†</td>
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<td>Describe exposure</td>
<td>Drug concentrations</td>
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<td>Assess ADAs of each agent</td>
<td>ADAs against IV treatments</td>
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<td>Further explore safety and tolerability</td>
<td>AESIs, ocular findings</td>
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<th>Secondary</th>
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<td>Objective</td>
<td>Assess clinical activity of belamaf at the recommended phase 2 dose in combination with other anti-cancer treatments vs belamaf monotherapy</td>
<td>Overall response rate†</td>
<td>Objective</td>
<td>Further assess clinical activity</td>
<td>CBR†, PFS, DoR, TTR, OS</td>
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<td>Further characterise safety</td>
<td>AEs, AESIs, ocular findings</td>
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<td>Evaluate plasma concentrations of belamaf and combination treatments</td>
<td>ADAs against IV treatments</td>
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<td>Drug concentrations</td>
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### Exploratory: dose escalation and cohort expansion

- Pharmacokinetics for each agent
- Bone marrow MRD status
- BCMA expression

- Pharmacodynamics (target engagement) markers and plasma soluble BCMA levels, among others, as candidate prognostic and predictive biomarkers
- Health-related quality of life (cohort expansion only)

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* Defined as Grade 3, 4 or 5 hematologic (febrile neutropenia or thrombocytopenia with clinically significant bleeding) or non-hematologic (except corneal AEs, Grade 3 or 4 nausea, vomiting, diarrhoea, or TLS resolving ≤7 days, or Grade 3 controlled hypertension). Grade 4 corneal toxicity, or liver/other organ toxicity meeting stopping criteria. † International Myeloma Working Group criteria. † ADA, anti-drug antibody; AE, adverse event; AESI, AE of special interest; BCMA, B-cell maturation antigen; CBR, clinical benefit rate; DoR, duration of response; IV, intravenous; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; TTR, time to response.
Patient Population

Key inclusion criteria

• Age ≥18 years
• Histologically or cytologically confirmed MM (IMWG criteria)
• Measurable disease (according to serum and/or urine M-protein and/or serum free light chain levels)
• ECOG Performance Status 0–2
• ≥3 prior lines of therapy (consisting of an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 mAb)
• Previous anti-BCMA targeted therapy allowed except prior belamaf or CAR T-cell therapy ≤3 months of screening
• History of autologous stem cell transplantation allowed if >100 days prior to screening and no active infections
• Acceptable haematological (neutrophil, haemoglobin and platelet), and vital organ (hepatic, cardiac and renal) function

Key exclusion criteria

• Current corneal epithelial disease (except mild punctate keratopathy)
• Current unstable liver or biliary disease
• Other malignancies (except those disease-free for >2 years or curatively treated non-melanoma skin cancer)
• Cardiovascular risk
• Active infection or HIV
• Recent history (≤6 months) of acute diverticulitis, inflammatory bowel disease, intra-abdominal abscess, GI obstruction
• Hepatitis B surface antigen or hepatitis B core antibody present, or positive for hepatitis C at screening or ≤3 months prior to first dose of study treatment
• Prior/concomitant therapy:
  • Previous belamaf treatment
  • Other mAbs within 30 days, systemic antimyeloma therapy or radiotherapy within 14 days, or plasmapheresis within 7 days of first dose of study drug
  • CAR T-cell therapy ≤3 months of screening
  • Prior allogeneic transplant
  • Major (except bone-stabilising) surgery ≤30 days from screening

BCMA, B-cell maturation antigen; ECOG, Eastern Cooperative Oncology Group; IMWG, International Myeloma Working Group; mAb, monoclonal antibody; MM, multiple myeloma;
Sub-study 1: Belamaf + GSK3174998

GSK3174998 is a humanised 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 regulatory T cells
  - This induces a T-cell mediated immune response against tumour cells (Figure)

- GSK3174998 has potential to overcome immune resistance and enhance immune-mediated antitumour activity
  - This activity is anticipated to be enhanced when combined with an agent causing immunogenic cell death, like belamaf

Preclinical data of belamaf plus a mouse OX40 surrogate antibody support the potential utility of combination therapy with belamaf and GSK3174998\(^1\)

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mAb, monoclonal antibody.
\(^1\) Montes de Oca R, et al. *EHA Library* 2019; 266357; PF558
Sub-study 2: Belamaf + GSK3359609

GSK3359609 is a humanised anti-ICOS Ig4 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 and member of the CD28 superfamily and plays an important role in the proliferation, differentiation, survival, and function of T cells

- GSK3359609 was designed and Fc-optimised to enhance T-cell function and enable antitumour responses without the depletion of ICOS-expressing cells (Figure)

The unique mechanistic profile of GSK3359609 as an ICOS agonist allows investigation of the antitumor potential of targeting a T-cell co-stimulator alone and in combination with belamaf

mAb, monoclonal antibody
Sub-study 3: Belamaf + nirogacestat

Nirogacestat (PF-03084014, SpringWorks Therapeutics) is a novel gamma-secretase inhibitor that prevents the cleavage of transmembrane proteins including Notch, APP and BCMA\(^1,2\)

- Gamma secretase has been found to cleave membrane-bound BCMA releasing it into the extracellular domain as soluble BMCA\(^2\), which may interfere with and limit efficacy of BCMA-directed therapy\(^3\)
- Inhibition of gamma secretase activity has been shown to increase cell-surface levels and availability of BCMA\(^2\) (Figure)

Preclinical data have shown synergistic effect of combining belamaf and nirogacestat, providing the rationale to support clinical evaluation of this combination in RRMM.\(^4\)

APP, amyloid precursor protein; BCMA, B-cell maturation antigen; RRMM, relapsed/refractory multiple myeloma.
Current status: All sub-studies are open to accrual

Acknowledgements
These findings have been previously presented\(^1\) and are included here with permission and on behalf of the original authors.

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Drug linker technology licensed from Seattle Genetics
Monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa

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1. Richardson P et al. ASH 2019; Poster 1857.