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

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Background

Unmet need

Patients with RRMM who have relapsed through multiple prior lines of therapy need novel, effective, targeted agents.[1]

Belantamab mafodotin

Belantamab mafodotin (belamaf; GSK2857916) is a first-in-class B-cell maturation antigen (BCMA)–binding, humanized, afucosylated, monoclonal antibody-drug conjugate (ADC).

BCMA is a cell-surface receptor expressed on multiple myeloma (MM) cells, absent on naïve and memory B cells, which promotes plasma cell survival.[2]

Belamaf has multimodal activity involving immune-independent ADC-mediated apoptosis and release of markers of ICD as well as immune-dependent mechanisms of action such as ADCC/ADCP (**Figure 1**).[3,4]

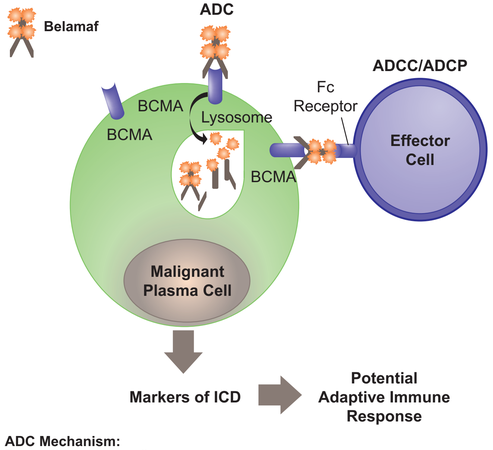
In the primary analysis of the pivotal, Phase II study (DREAMM-2; NCT03525678),[5] single-agent **belamaf** demonstrated deep and durable clinical responses (32% and 35% overall response rate [ORR]) in the 2.5-mg/kg and 3.4-mg/kg cohorts, respectively), with an acceptable safety in patients with heavily pretreated MM, with 13 months' follow-up.[6]

Combination strategies

Combining **belamaf** with **agents with other mechanisms of action** has the potential to achieve synergistic effects in MM, thereby enhancing efficacy.

Belamaf is being evaluated in clinical trials in various **combination strategies**, in addition to evaluation as monotherapy (see oral presentation no. 8502, and poster nos. 419, 436, 441, and 456 at this meeting).

Figure 1. Multimodal mechanisms of action of belantamab mafodotin (GSK2857916)



ADC Mechanism:
Targets dividing tumor cells

ADCC/ADCP Mechanism:
Targets dividing and non-dividing tumor cells

ICD Mechanism:
Dying tumor cells expose antigens which engage patient's own immune system

Methods

Study design

Phase I/II

The DREAMM-5 platform trial (Study 208887; NCT04126200) is a randomized, open-label phase 1/2 study utilizing a master protocol to allow evaluation of multiple **belamaf-containing** combinations against a shared **belamaf** monotherapy control arm (**Figure 2**).

- Platform trials are designed to study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to be added or removed from the platform based on the results from an algorithm[6]
- The advantage of platform trials is they allow direct comparisons between competing therapies or can be structured to evaluate different treatments to their respective controls in parallel[7,8]

In the cohort expansion (CE) phase, participants will be randomized first to a sub-study then within a sub-study to either investigational **combination treatment** or shared **belamaf** monotherapy control arm until 35 participants have been assigned to the combination treatment.

Participants will also be stratified by number of prior lines of therapy (3–4 vs >4).

The dose exploration (DE) phase of each sub-study will evaluate the safety, tolerability and clinical activity of escalating doses and identify a recommended Phase 2 dose (RP2D) for each investigational **belamaf combination** treatment.

Starting doses for each agent will be selected based on findings from previous monotherapy studies.

Sub-studies may additionally involve dose-escalation or de-escalation cohort(s), guided by a modified toxicity probability interval method.[9]

Figure 2. Study design

Participants in both DE and CE will continue dosing and disease evaluations until disease progression, unacceptable toxicity, death, start of new anti-cancer treatment, withdrawal of consent or end of study.

Study objectives

DE phase

- **Primary:** to determine the safety and tolerability of **belamaf** in combination with other **anti-cancer treatments** and establish the RP2D for the combination treatment in each sub-study.
- **Key secondary:** to evaluate clinical measures of efficacy per combination
- **Other secondary:** to describe exposure and assess anti-drug antibodies (ADAs) of each drug, and further explore safety and tolerability

CE phase

- **Primary:** to assess the efficacy of **belamaf** at the RP2D in combination with other **anti-cancer treatments** vs belamaf monotherapy.
- **Secondary:** to further assess the clinical activity of the combination regimen vs belamaf monotherapy, to further characterize the safety of the combination regimen and to evaluate plasma concentrations and ADA (if applicable) of **belamaf** and **combination treatments** in participants within each sub-study.

Exploratory (both phases)

- To characterize pharmacokinetic parameters for each agent, to evaluate bone marrow minimal residual disease (MRD) status, BCMA expression, pharmacodynamic (target engagement) markers and serum-soluble BCMA levels, among others, as candidate prognostic and predictive biomarkers and to characterize the health-related quality of life (HRQoL) (CE only).

Study endpoints

Endpoints for the DE and CE phases of DREAMM-5

	Primary endpoints	Secondary endpoints	Exploratory endpoints
DE phase	• DLTs* • AEs	• ORR (IMWG criteria)[8] • Drug concentrations • ADAs against IV treatments • AESIs, ocular findings	• PK parameters • CBR,[8] DoR, TTR, PFS, OS • Biomarkers • Pharmacogenomics • MRD negativity in patients with ≥VGPR
CE phase	• ORR (IMWG criteria)[8]	• CBR,[8] DoR, TTR, PFS, OS • AEs, AESIs, ocular findings • ADAs against IV treatments • Drug concentrations	• PK parameters • HRQoL • Biomarkers • Pharmacogenomics • MRD negativity in patients with ≥VGPR

*DLTs defined as events attributed to either or both study agents that meet at least one of the following criteria: hematologic: Grade 3, 4 or 5 events (febrile neutropenia or thrombocytopenia with clinically significant bleeding); Grade 3, 4 or 5 non-hematologic except Grade 3 or 4 nausea, vomiting, or diarrhea controlled with symptomatic treatment, Grade 3 or 4 TLS resolving ≤7 days, Grade 3 controlled hypertension, Grade 4 (GSK scale) corneal toxicity, or liver/other organ toxicity meeting stopping criteria.

Follow up and analysis

The primary analysis in CE will be 6 months after last participant's first dose for each sub-study.

A **combination treatment** will be considered superior to **belamaf** monotherapy in ORR if the posterior probability is ≥90% for combination response rate being greater than **belamaf** monotherapy.

For each sub-study, the IA will be performed in the DE phase after all DE participants in the sub-study have progressed/died, discontinued study intervention, or have had 3 efficacy assessments (1 baseline and 2 post-baseline assessments).

Key inclusion criteria

- Age ≥18 years
- Histologically or cytologically confirmed MM (IMWG criteria)[9,10]
- Measurable disease (according to serum and/or urine M-protein and/or serum free light chain levels)
- ECOG PS 0–2
- ≥3 prior lines of therapy (consisting of an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 mAb)
  - History of autologous SCT allowed if >100 days prior to screening and no active infections
- Acceptable hematologic (neutrophil, hemoglobin 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)
- CV 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 belantamab mafodotin treatment
  - Other mAbs ≤30 days, systemic antimyeloma therapy or radiotherapy ≤14 days, or plasmapheresis ≤7 days of first dose of study drug
  - CAR T-cell therapy ≤3 months of screening
  - Prior allogeneic transplant
  - Major (except bone-stabilizing) surgery ≤30 days from screening

Sub-studies

Ongoing sub-studies include combinations with **the following agents**, selected based on scientific rationale and/or results from preclinical experiments in **combination** with **belamaf**:

Sub-study 1

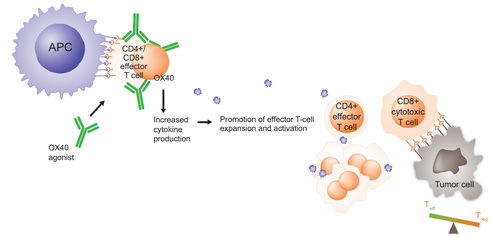
OX40 signaling promotes effector T-cell proliferation and survival, while blocking the suppressive function of regulatory T cells; this induces a T-cell mediated immune response against tumor cells (**Figure 3**).[12]

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.

GSK3174998 has potential to overcome immune resistance and enhance immune-mediated antitumor activity; this activity is anticipated to be enhanced when combined with an agent causing ICD, like **belamaf**.

Preclinical data combining **belamaf** with a mouse OX40 surrogate antibody supports this hypothesis.[13]

Figure 3. GSK3174998 a humanized wild-type IgG1 anti-OX40 agonistic mAb



Sub-study 2

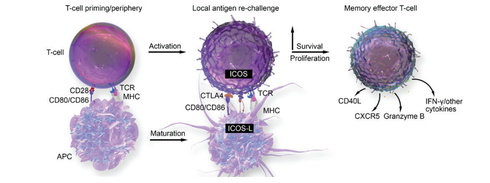
ICOS is a co-stimulatory receptor and member of the CD28 superfamily; it plays an important role in the proliferation, differentiation, survival, and function of T cells.[14]

GSK3359609 is a humanized anti-ICOS Ig4 mAb selected for its nanomolar binding to and agonist activity in ICOS-expressing CD4+ and CD8+ effector T cells.

GSK3359609 was designed and Fc-optimized to enhance T cell function and enable antitumor responses without the depletion of ICOS-expressing cells (**Figure 4**).

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**.

Figure 4. GSK3359609, a T-cell activating anti-ICOS IgG4 inducible T-cell costimulatory agonist antibody



Sub-study 3

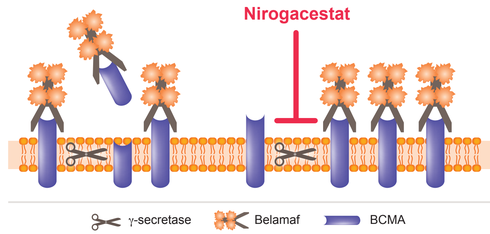
Nirogacestat (PF-03084014, SpringWorks Therapeutics) is a novel gamma-secretase inhibitor that prevents the cleavage of transmembrane proteins including Notch, APP and BCMA[1,2]

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 5**)

Preclinical data have shown a synergistic effect of combining **belamaf** and **nirogacestat**, providing the rationale to support clinical evaluation of this combination in RRMM.[4]

Figure 5. Nirogacestat (PF-03084014, SpringWorks Therapeutics) MoA



Current status

Sub-studies 1 and 2 are open to accrual; Sub-study 3 opening Q2/Q3 2020

Abbreviations

ACS, acute coronary syndrome; ADAs, anti-drug antibodies; ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody dependent cellular phagocytosis; AEs, adverse events; AESI, adverse events of special interest; BCMA, B-cell maturation antigen; Belamaf, belantamab mafodotin; CAR, chimeric antigen receptor; CBR, clinical benefit rate; CE, cohort expansion; CI, confidence interval; CR, complete response; CV, cardiovascular; DE, dose exploration; DLTs, dose-limiting toxicities; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; HF, heart failure; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; IA, interim analysis; ICD, immunogenic cell death; IMWG, International Myeloma Working Group; IV, intravenous; mAb, monoclonal antibody; MI, myocardial infarction; MM, multiple myeloma; MoA, mechanism of action; MRD, minimal residual disease; NYHA, New York Heart Association; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; SCT, stem cell transplantation; TLS, tumor lysis syndrome; TTP, time to progression

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