Presentation 16

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

Paul Richardson[1], Beata Holkova[2], Nicola Jackson[3], Thelma Netherway[3], Maria Brouch[2], Sofia Paul[2], Geraldine Ferron-Brady[2], Anne Yeakey[4], Chris Shelton[2], Rocio Montes de Oca[2], L. Mary Smith[5], Chris Ahlers[2], Marc Ballas[2], Elaine Paul[4], Ira Gupta[2]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]GlaxoSmithKline, Upper Providence, PA, USA; [3]GlaxoSmithKline, Stockley Park, UK; [4]GlaxoSmithKline, Research Triangle Park, NC, USA; [5]SpringWorks Therapeutics Inc., Stamford, CT, USA

Disclosures

Presenting author: IG is an employee of and holds stocks and shares in GlaxoSmithKline and holds stocks and shares in Novartis.

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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]

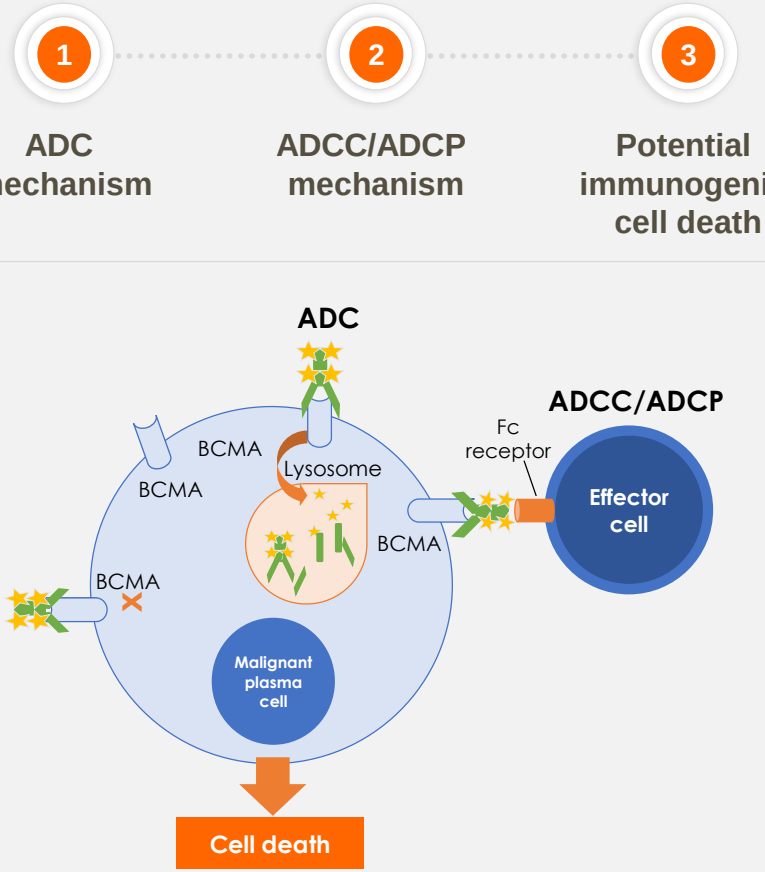
Belantamab mafodotin (belamaf; GSK2857916)

- First-in-class anti-BCMA antibody-drug conjugate with multimodal mechanisms of action[2] (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[3-6]

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

Belamaf Mechanisms of Action[7]



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

1. Gandhi UH, et al. *Leukemia* 2019;33:2266. 2. Tai YT, et al. *Blood* 2014;123:3128. 3. Trudel S et al. *Lancet Oncol* 2018;19:1641 4. Trudel S et al. *Blood Cancer J* 2019;9:37; 5. Lonial S et al. *Lancet Oncol* 2020;21:207. 6. Lonial S et al, COMy 2020, Oral 32; 7. Richardson P et al. ASH 2019; Poster 1857

DREAMM-5 Study Design

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

N≤10 per dose level — **Sub-study 1**: Belamaf + GSK3174998

N≤10 per dose level — **Sub-study 2**: Belamaf + GSK3359609

N≤10 per dose level — **Sub-study 3**: Belamaf + Nirogacestat

N≤10 per dose level — **Sub-study 4**: Belamaf + D

More sub-studies can be added

Interim analysis based on ORR to determine

1. Whether to proceed to cohort expansion
2. RP2D

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

Belamaf monotherapy control arm

N≤35 — **Sub-study 1**: Belamaf RP2D + GSK3174998

N≤35 — **Sub-study 2**: Belamaf RP2D + GSK3359609

N≤35 — **Sub-study 3**: Belamaf RP2D + Nirogacestat

N≤35 — **Sub-study 4**: Belamaf RP2D + D

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

Dose escalation

Primary		Secondary	
Objective	**Endpoints**	**Objectives**	**Endpoints**
Assess safety and tolerability of belamaf in combination with other anti-cancer treatments and establish recommended phase 2 dose	Dose-limiting toxicities* AEs	Evaluate clinical efficacy measures Describe exposure Assess ADAs of each agent Further explore safety and tolerability	Overall response rate† Drug concentrations ADAs against IV treatments AESIs, ocular findings

Cohort expansion

Primary		Secondary	
Objective	**Endpoints**	**Objectives**	**Endpoints**
Assess clinical activity of belamaf at the recommended phase 2 dose in combination with other anti-cancer treatments vs belamaf monotherapy	Overall response rate†	Further assess clinical activity Further characterise safety Evaluate plasma concentrations of belamaf and combination treatments	CBR[1], PFS, DoR, TTR, OS AEs, AESIs, ocular findings ADAs against IV treatments Drug concentrations

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)

* 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.[1] 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)[1]
- 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

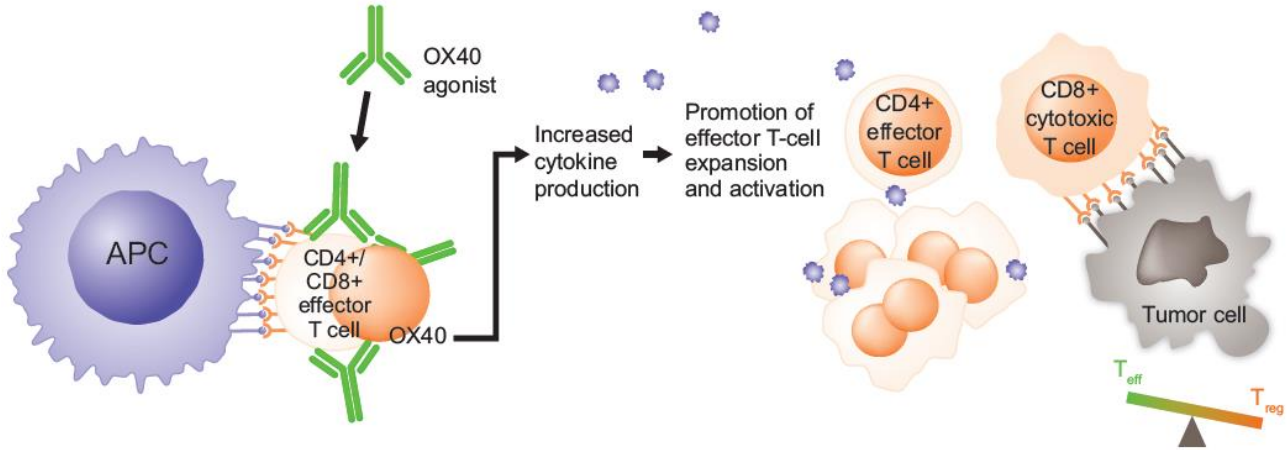
- Current corneal epithelial disease (except mild punctate keratopathy)
- Current unstable liver or biliary disease
- Other malignancies (except those disease-free for >2 years or curatively treated non-melanoma skin cancer)
- Cardiovascular risk
- Active infection or HIV
- Recent history (≤6 months) 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]

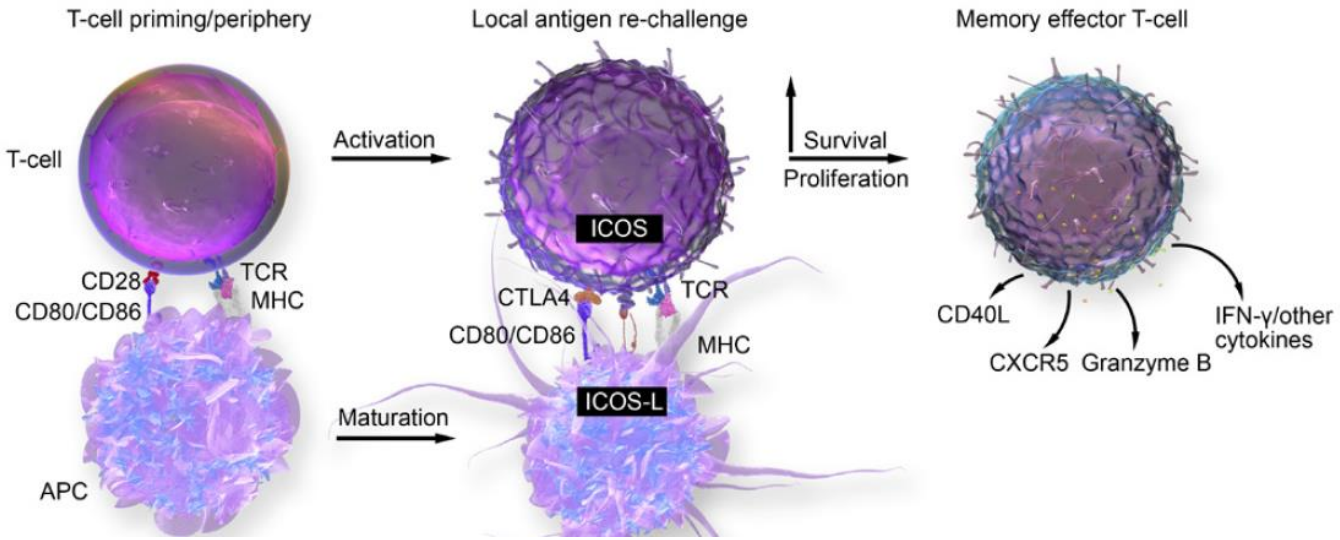
mAb, monoclonal antibody.

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[1]
- 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

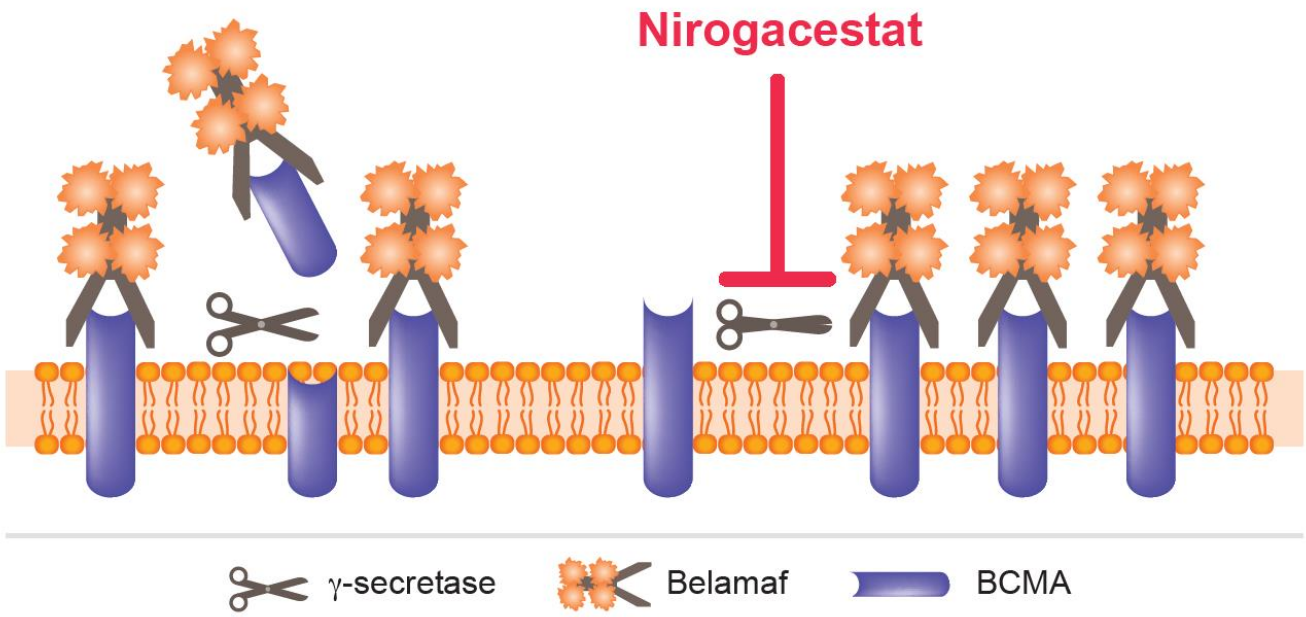
mAb, monoclonal antibody

1. Hutloff A, et al. Nature 1999;397:263–6

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.

1. Lanz TA, et al. *J Pharmacol Exp Ther* 2010;334:269. 2. Laurent SA, et al. *Nat Comm* 2015; 6:7333. 3. Pont MJ, et al. *Blood* 2019; 134:1585. 4. Eastman S, et al *Blood* 2019; 134Supplement_14401 doi

Current status: All sub-studies are open to accrual

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Drug linker technology licensed from Seattle Genetics

Monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa

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