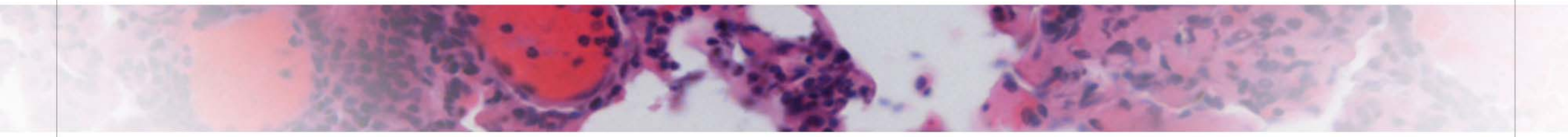
American Society of Hematology
Helping hematologists conquer blood diseases worldwide



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

Paul Richardson,[1] Ajay Nooka,[2] Hang Quach,[3] Suzanne Trudel,[4] David Routledge,[5,6] Kevin Song,[7] Hareth Nahi,[8] Sofia Paul,[9] Josephine Khan,[10] Maria Brouch,[9] Geraldine Ferron-Brady,[9] Anne Yeakey,[11] Chris Shelton,[9] Rocio Montes de Oca,[9] L. Mary Smith,[12] Ellie Im,[13] Christoph M. Ahlers,[9] Elaine M. Paul,[11] Beata Holkova,[9] Ira Gupta,[9] Brandon E. Kremer,[13] Paula Rodriguez Otero[14]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [3]University of Melbourne, St. Vincent's Hospital Melbourne, Melbourne, VIC, Australia; [4]Princess Margaret Cancer Centre, Toronto, ON, Canada; [5]Department of Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia; [6]Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia; [7]Vancouver General Hospital, Vancouver, BC, Canada; [8]Karolinska University Hospital: Stockholm, Sweden; [9]GlaxoSmithKline, Upper Providence, PA, USA; [10]GlaxoSmithKline, Stevenage, UK; [11]GlaxoSmithKline, Research Triangle Park, NC, USA; [12]SpringWorks Therapeutics Inc., Stamford, CT, USA; [13]GlaxoSmithKline, Waltham, MA, USA; [14]Clínica Universidad de Navarra-Pamplona, Navarra, Spain

Poster No. 2299 | Presented at the 62nd American Society of Hematology Annual Meeting and Exposition (Virtual Format) | December 5–8, 2020

Background

Unmet need

Patients with heavily pre-treated RRMM have a poor prognosis; novel, well-tolerated treatments that induce lasting responses are warranted[1,2]

Belantamab mafodotin (belamaf; BLENREP)

- First-in-class anti-BCMA antibody-drug conjugate with multimodal mechanism of action[2] (**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-up[4,5]

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-studies[5,6]

Belamaf Mechanisms of Action*

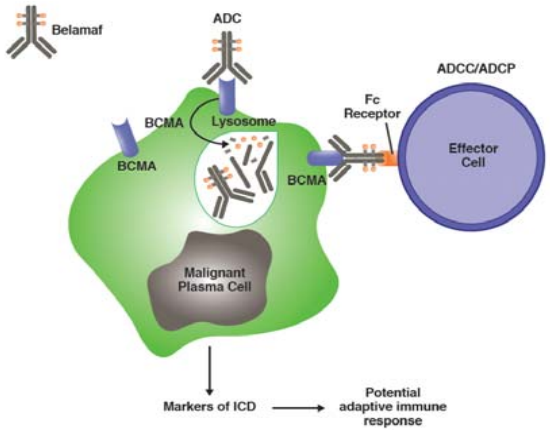


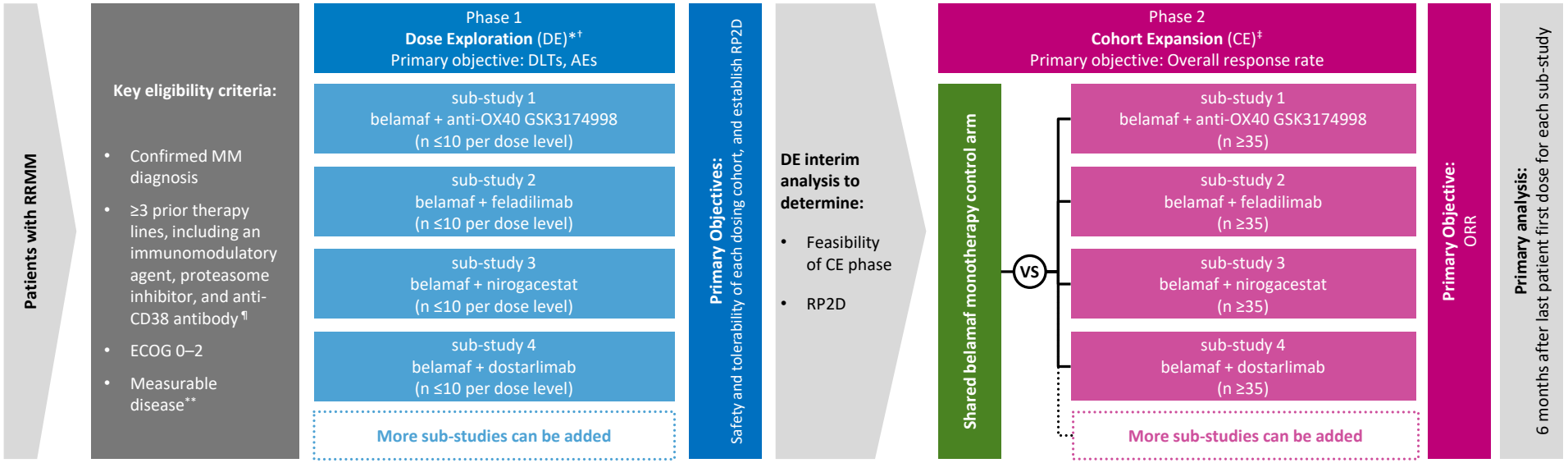
*Image adapted from Richardson P, et al. Presented at the 61st Annual Meeting of the American Society of Hematology, December 7–10, 2019, Orlando, FL. Poster 1857.

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

1. Gandhi UH, et al. *Leukemia.* 2019;33:2266–75; 2. Chari A, et al. *N Engl J Med.* 2019;381:727–38; 3. Tai YT, et al. *Blood.* 2014;123:3128–38; 4. Montes de Oca R, et al. EHA Library. 2019; 266357; PF558; 5.Lonial S, et al. *Lancet Oncol.* 2020;21:207–21; 6. Lonial S, et al. ASCO Poster 436; 7. Woodcock J and LaVange LM. *N Engl J Med.* 2017:377;62–70; 8. Saville BR and Berry SM. *Clin Trials.* 2016:13;358–366.

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 belamaf-containing combinations will be evaluated in separate sub-studies to identify efficacious doublet combinations, vs a shared belamaf monotherapy control arm



*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

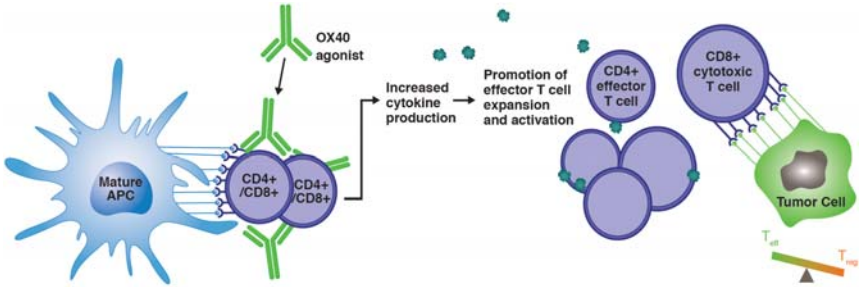
OX40 signalling promotes effector T-cell proliferation and survival, while blocking the suppressive function of T_{reg} cells

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[1]

GSK3174998 Mechanism of Action



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[1] potentially leading to an adaptive immune response

APC, antigen-presenting cell; DC, dendritic cells; ICD, immunogenic cell death; IgG, immunoglobulin G; mAb, monoclonal antibody; T_{reg}, regulatory T cell.

1. Montes de Oca R, et al. EHA Library. 2019; 266357; PF558.

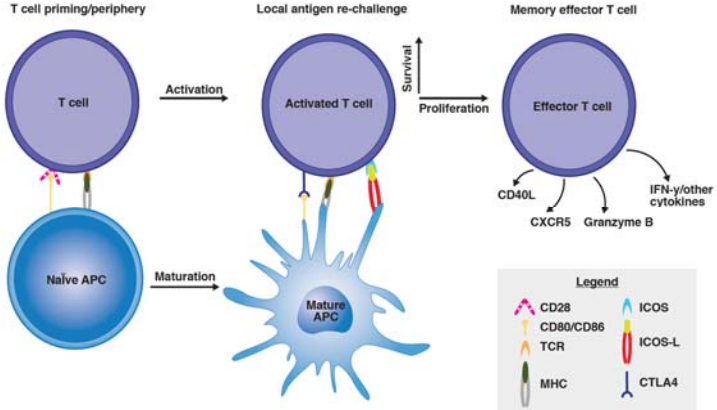
Sub-study 2: Belamaf + Feladilimab

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[1]

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

Feladilimab Mechanism of Action



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.

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

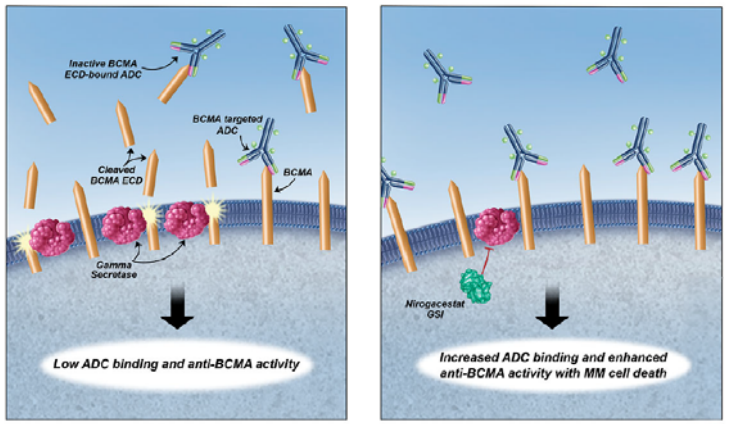
Sub-study 3: Belamaf + Nirogacestat

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

Gamma secretase has been found to cleave membrane-bound BCMA, releasing the extracellular domain as sBCMA into circulation,[2] which interferes with and limits efficacy of BCMA-directed therapies[3]

Inhibition of gamma secretase activity has been shown to increase cell-surface levels and availability of BCMA and reduce sBCMA in circulation[2] (**Figure**)

Belamaf + Nirogacestat Combined Mechanism of Action*



Pre-clinical data have shown synergistic effects of combining belamaf and nirogacestat, providing the rationale to support clinical evaluation of this combination in RRMM[4]

*Figure taken from Springworks Therapeutics, with permission. © Springworks Therapeutics, all rights reserved.
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.
1. Lanz TA, et al. *J Pharmacol Exp Ther.* 2010;334:269–77; 2. Laurent SA, et al. *Nat Comm.* 2015;6:7333–45; 3. Pont MJ, et al. *Blood.* 2019;134:1585–97; 4. Eastman S, et al. *Blood.* 2019;134(Suppl 1):4401.

Sub-study 4: Belamaf + Dostarlimab

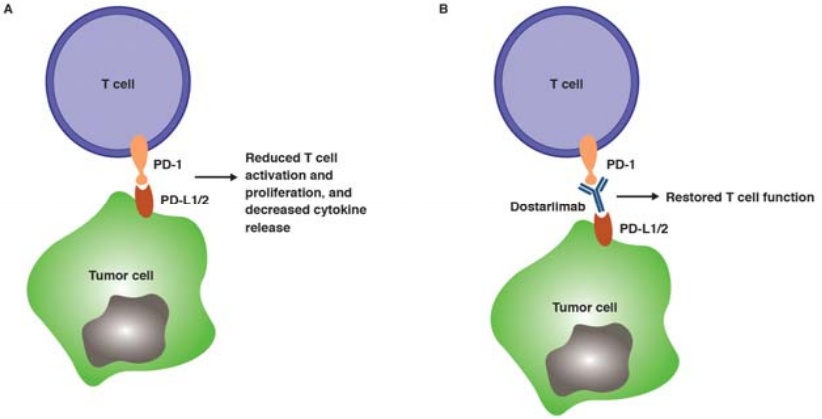
Dostarlimab is a humanized anti-PD-1 IgG4 mAb that blocks interactions between PD-1 and PD-L1 or PD-L2[1]

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[1-5] (**Figure**)

Early clinical data with dostarlimab showed encouraging anti-tumor activity in patients with endometrial cancer[6]

Expression of PD-1 and its ligands has been demonstrated in MM[7,8]

Dostarlimab Mechanism of Action



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.

1. Chen Y, et al. *Front Immunol.* 2020;11:1088–101; 2. McLaughlin J, et al. *JAMA Oncol*. 2016;2:46–54; 3. Ahmadzadeh M, et al. *Blood*. 2009;114:1537–44; 4. Konishi J, et al. *Clin Cancer Res*. 2004;10:5094–100; 5. Hamanishi J, et al. *Proc Natl Acad Sci USA*. 2007;104:3360–5; 6. Oaknin A, et al. SGO Annual Meeting. Honolulu, HI: *Annals Oncol*. 2019:viii332-viii58; 7. Atanackovic D, et al. *Leukemia*. 2014;28:993-1000; 8. Benson DM, et al. *Blood*. 2010;116:2286-94.

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)

MM, multiple myeloma

Disclosures and Acknowledgments

PR: consultancy from AbbVie, Celgene, GlaxoSmithKline, and Takeda, research funding from Takeda, honoraria from Celgene, GlaxoSmithKline, Janssen, and Takeda, and travel expenses from GlaxoSmithKline, Janssen, and Takeda. **AN**: consultancy from Adaptive Technologies, Amgen, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Janssen Oncology, Karyopharm Therapeutics, Oncopeptides, Sanofi, and Takeda; research funding from Amgen, Janssen Oncology, and Takeda; personal fees from GlaxoSmithKline. **HQ**: consultancy and honoraria from Amgen, Celgene, GlaxoSmithKline, Janssen Cilag, and Karyopharm; research funding from Amgen, Celgene, and Sanofi. **ST**: consultancy from Amgen, Celgene, and GlaxoSmithKline; research funding from Amgen, Celgene, GlaxoSmithKline, Janssen, and Genentech; honoraria from Amgen Canada, Celgene, Janssen, Karyopharm, Sanofi, and Takeda. **DR**: consultancy from Celgene and Sandoz; honoraria from Amgen, Bristol-Myers Squibb, Celgene, and Sandoz. **KS**: consultancy from Amgen, Celgene, and Takeda; research funding from Celgene and Janssen; honoraria from Amgen, Celgene, Janssen, Otsuka, and Takeda. **HN** has no conflicts to declare. **SP**, **JK**, **MB**, **G F-B**, **AY**, **CS**, **RMdO**, **EI**, **CMA**, **EMP**, **BK**, **IG**, **BEK** and **PRO** are employees of GlaxoSmithKline, with ownership interest. **LMS** is an employee of SpringWorks Therapeutics, with ownership interest.

Sub-studies 1, 2, and 3 have been previously presented[1,2]

This study was funded by GSK (208887). Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa

Editorial assistance was provided by Martina Stagno D'Alcontres of Fishawack Indicia Ltd and funded by GSK

Please find the online version of this poster by scanning the QR (Quick Response) code or via http://tago.ca/ash5

Presenting author contact: Paul_Richardson@dfci.harvard.edu

1. Richardson P, et al. ASH 2019; Poster 1857; 2. Richardson P, et al. ASCO 2020; Poster 452.