Clinical Trial Protocol

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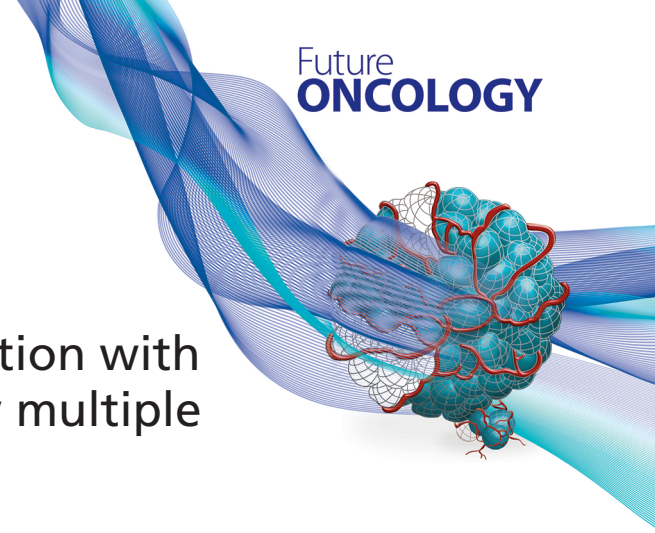

Belantamab mafodotin in combination with novel agents in relapsed/refractory multiple myeloma: DREAMM-5 study design

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Belantamab mafodotin (belamaf) is a BCMA-targeted antibody–drug conjugate recently approved as monotherapy for adults with relapsed/refractory multiple myeloma who have received ≥4 prior therapies. Belamaf binds to BCMA and eliminates myeloma cells by multimodal mechanisms of action. The cytotoxic and potential immunomodulatory properties of belamaf have led to novel combination studies with other anticancer therapies. Here, we describe the rationale and design of DREAMM-5, an ongoing Phase I/II platform study evaluating the safety and efficacy of belamaf combined with novel agents, including GSK3174998 (OX40 agonist), feladilimab (an ICOS; GSK3359609), nirogacestat (a gamma-secretase inhibitor; PF-03084014) and dostarlimab (a PD-1 blocker) versus belamaf monotherapy for patients with relapsed/refractory multiple myeloma.

Clinical trial registration: NCT04126200 (ClinicalTrials.gov).

First draft submitted: 15 December 2020; Accepted for publication: 29 January 2021; Published online: 8 March 2021

Keywords: antibody–drug conjugate • BCMA • belantamab mafodotin • clinical trial • dostarlimab • feladilimab • GSK3174998 • multiple myeloma • nirogacestat • platform study

Multiple myeloma (MM) is an incurable plasma cell disorder caused by the proliferation of malignant plasma cell clones in the bone marrow, which ultimately results in end-organ dysfunction [1,2]. MM accounted for 1.2% of all cancer diagnoses and 1.6% of all cancer deaths in Europe (2018) and 1.8 and 2.1% in the US (2020), respectively [1,3].

Through the use of immunomodulatory agents and proteasome inhibitors (PI) sequentially with autologous stem-cell transplantation and significant improvements in supportive care strategies, the median overall survival (OS) of patients with MM has almost doubled in the past two decades, with comparable improvements also seen in the transplant-ineligible population [4–7]. In addition, the introduction of anti-CD38 monoclonal antibodies (mAbs), such as daratumumab, and antisignaling lymphocytic activation molecule family member seven antibody elotuzumab, used alone or in combination with immunomodulatory agents and PIs, has further enhanced response and improved survival rates in patients with MM, including in those with relapsed or refractory MM (RRMM) [6,8–10].

Despite these therapeutic advances, MM remains a challenging and incurable disease, with almost all patients experiencing relapse and eventually becoming refractory to available therapies [11–16]. Prognosis worsens and the duration of remission reduces with each subsequent line of treatment. Although newer interventions and combinations are being developed to improve patient survival and quality of life (QoL), and to deepen and extend the duration of treatment responses, an urgent requirement for novel targets and therapeutic modalities for the effective treatment of RRMM remains [17]. Combining therapies with complementary modes of action may be a solution to address this high unmet need, either through combining the current standard of care (SoC) therapies with novel therapies, or novel agents with other novel agents.

Master protocol trials

Traditional clinical trials are often designed to evaluate a single treatment in a homogenous patient population but are often not able to address multiple questions within a single protocol. This has led to the development of new, more efficient clinical trial design strategies that allow multiple treatments to be evaluated in one or more patient populations or disease to help expedite development of oncology drugs, including biologics [18]. This novel trial design is implemented through a master protocol encompassing multiple substudies designed to answer several questions or hypotheses in parallel, with each substudy incorporating research objective(s) common to the entire study as well as specific to each substudy. Included under the broad definition of a master protocol are three distinct entities: umbrella, basket and platform trials.

These three trial strategies all include a collection of substudies that share key design components and methods, allowing better coordination than what can be achieved in multiple single trials designed and conducted independently. An umbrella trial is designed to study multiple targeted therapies in the context of a single disease [18]. Typically, patients with the disease are screened for the presence of a biomarker or other characteristic and then assigned to a substudy. A basket trial evaluates a single targeted therapy in target-positive patients in the context of multiple diseases or disease subtypes [18]. A master protocol for a basket trial could contain multiple substudies that test various biomarker–drug pairs. Finally, a platform trial investigates multiple targeted therapies in the context of a single disease against a common control group [18]. Platform trials are ongoing over time, with no fixed end date. They are governed by a master protocol that has prespecifed adaptation rules to allow for the addition of new treatment paradigms as novel therapies emerge, and for ineffective interventions to be ceased on the basis of a decision algorithm. Additionally, this trial design allows expansion of combinations with the most promising efficacy and safety. Platform trials are more dynamic than other types of master protocols and are particularly useful to study treatment combinations and for direct comparisons between competing treatments [19]. They are also designed to find effective treatments more rapidly and with fewer resources compared with traditional clinical trial designs [19]. The trial structure can be complex, can present contracting challenges and regulatory issues, and may require multiple protocol amendments [20,21].

Belantamab mafodotin

BCMA is a member of the TNF receptor superfamily, which is ubiquitously expressed on the surface of normal plasma cells and late-stage B cells as well as on malignant plasma cells in all patients with MM and other B-cell malignancies [22,23]. BCMA promotes maturation and long-term survival of normal plasma cells and is essential for proliferation and survival of malignant plasma cells in MM [23]. Belantamab mafodotin (belamaf; GSK2857916; BLENREP) is an antibody–drug conjugate consisting of a humanized, afucosylated immunoglobulin G1 (IgG1) anti-BCMA mAb conjugated to the cytotoxic payload MMAF by a protease-resistant maleimidocaproyl cysteine linker [24]. Belamaf specifically binds BCMA and eliminates MM cells by a multimodal mechanism of action. This includes delivering MMAF to BCMA-expressing malignant cells, resulting in inhibition of BCMA-receptor signal-

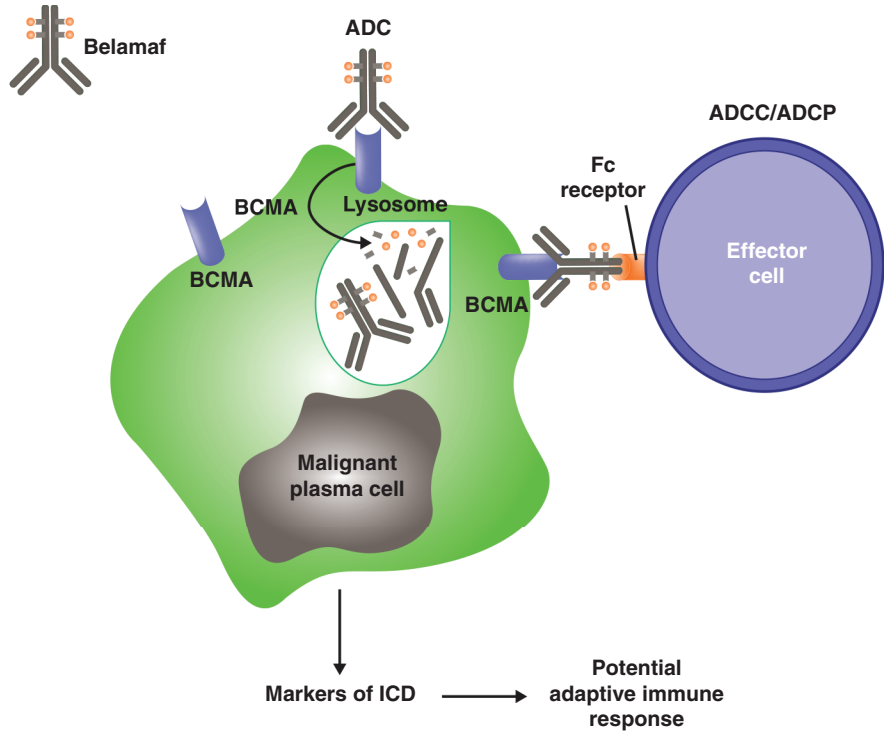

Figure 1. Multimodal mechanism of action of belamaf (GSK2857916).
ADC: Antibody–drug conjugate; ADCC: Antibody-dependent cellular cytotoxicity; ADCP: Antibody-dependent cellular phagocytosis; Belamaf: Belantamab mafodotin; Fc: Fragment crystallizable; ICD: Immunogenic cell death.
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ing and microtubule polymerization, leading to apoptosis; induction of antibody-dependent cellular cytotoxicity and phagocytosis (ADCC/ADCP, respectively); and the release of markers characteristic of immunogenic cell death (ICD), potentially leading to an adaptive immune response and immunologic memory (Figure 1) [24,25].

As part of the Driving Excellence in Approaches to Multiple Myeloma (DREAMM) clinical program, the Phase I DREAMM-1 study (NCT02064387) was conducted in patients with RRMM previously exposed to alkylators, PIs and immunomodulatory agents, who were refractory to their last line of treatment. The study demonstrated that belamaf 3.4 mg/kg monotherapy had a manageable safety profile and was associated with a 60% overall response rate (ORR) (43% in daratumumab-refractory patients), a median duration of response (DoR) of 14.3 months and a progression-free survival (PFS) of 12 months [27,28]. In the subsequent Phase II DREAMM-2 study (NCT03525678), single-agent belamaf was evaluated in patients with RRMM treated with ≥3 prior lines of therapy, who were refractory to a PI, refractory to an immunomodulatory agent, and refractory or intolerant to an anti-CD38 mAb [29]. The primary analysis of DREAMM-2 demonstrated deep and durable responses in this heavily pretreated population (median number of 7 prior lines of therapy), which were sustained at 13 months of follow-up with belamaf 2.5 mg/kg [29]. The ORR was 32%, median DoR was 11.0 months, median PFS was 2.8 months and median OS was 13.7 months [29,30]. Belamaf 2.5 mg/kg had comparable efficacy with 3.4 mg/kg and better safety profile than the higher dose. Based on these data, belamaf obtained US and EU approval for use in adults with RRMM treated with ≥4 prior therapies, including an anti-CD38 mAb, a PI and an immunomodulatory agent [31,32]. In addition, a lyophilized preparation of belamaf (intended for future use), evaluated as part of DREAMM-2, was both well tolerated and active, thus enhancing belamaf's ulility in the real world setting and providing a more practical preparation for administration [33].

Combining belamaf with agents that have a different mechanism of action may lead to additive or synergistic effects in MM and may provide additional benefits to patients [25]. Clinical trials evaluating belamaf in combination

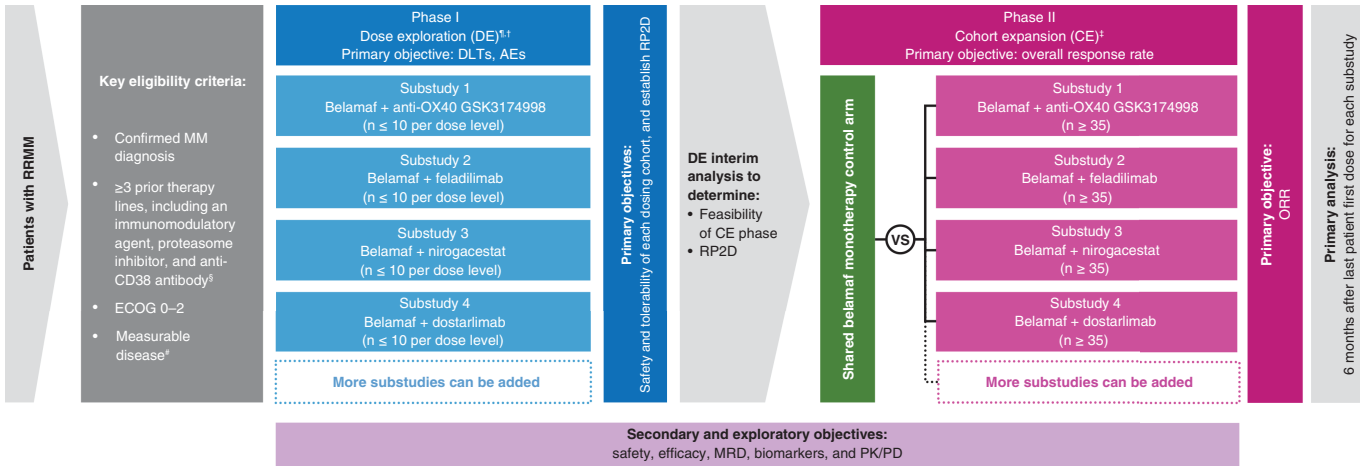

Figure 2. DREAMM-5 study design.
†Assignment to a substudy in DE will be according to treatment slot availability. When more than one substudy or dose level is enrolling, allocation will be by a predetermined algorithm.
‡Participants in CE are stratified by substudy and prior lines of therapy (3–4 vs >4).
§Prior anti-BCMA therapy is permitted.
¶Substudies may include dose-escalation or de-escalation cohort(s) guided by modified toxicity probability interval principles.
#As measured by serum and/or urine M-protein and/or serum-free light chain levels.
AE: Adverse event; CE: Cohort expansion; DE: Dose exploration; DLT: Dose-limiting toxicity; dostarlimab, a PD-1 blocker; DREAMM: Driving Excellence in Approaches to Multiple Myeloma; ECOG: Eastern Cooperative Oncology Group; feladilimab, an ICOS agonist; MRD: Minimal residual disease; nirogacestat, a gamma-secretase inhibitor; ORR: Overall response rate; PD: Pharmacodynamic; PK: Pharmacokinetic; RP2D: Recommended Phase II dose; RRMM: Relapsed/refractory multiple myeloma.
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with SoC treatments are being explored, including belamaf combinations with lenalidomide and dexamethasone (DREAMM-6 study), bortezomib and dexamethasone (DREAMM-6 and DREAMM-7 studies), bortezomib, lenalidomide and dexamethasone (DREAMM-9), and pomalidomide and dexamethasone (DREAMM-8 study) [34–38]. Additionally, combinations of belamaf with other anticancer agents, such as in combination with pembrolizumab (DREAMM-4 study) are being investigated [39]. Here, we present the rationale and study design of the innovative DREAMM-5 platform trial, evaluating combinations of belamaf with other anticancer agents, including novel agents GSK3174998 (an OX40 agonist mAb), feladilimab (an ICOS agonist mAb, GSK3359609), nirogacestat (a small molecule gamma-secretase inhibitor, PF-03084014) and dostarlimab (an anti-PD-1 mAb, GSK4057190). The aim of the study is to identify safe and effective belamaf combinations for the treatment of RRMM.

Design

Study design & treatment

The DREAMM-5 (NCT04126200) platform trial is a global Phase I/II multicenter study that incorporates an efficient design in one master protocol, wherein multiple belamaf-containing novel combinations will be evaluated in separate substudies to identify effective combinations versus a shared belamaf monotherapy control arm (Figure 2). Each substudy is defined as the data collected in the dose exploration (DE) and cohort expansion (CE) phase for each combination treatment arm together with the control arm. Substudy combination treatments will be individually assessed for safety and efficacy in both the DE and CE phases.

The DE phase for each arm will evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), biomarkers and clinical activity of the investigational belamaf combination treatment. Starting doses will be selected based on findings from previous monotherapy studies for belamaf (1.9 mg/kg starting dose up to a maximum potential dose of 2.5 mg/kg unless otherwise specified in the substudy) and the combination treatment [29]. For each substudy, the DE phase will consist of multiple cohorts exploring different doses of belamaf and the combination partner. Substudies may additionally involve one or more dose-escalation or de-escalation cohort(s). An interim analysis will be made at the end of the DE to determine the feasibility of progressing each combination to the CE phase and to select the recommended Phase II dose (RP2D) for each combination based on the accrued clinical safety and laboratory assessments, PK, PD and efficacy data.

In the CE phase for each substudy, patients will be randomized to an investigational combination treatment or a shared belamaf monotherapy control arm. Patients in the CE phase of each substudy will be stratified by number of prior therapies (3–4 vs >4 prior therapies). The control arm will be belamaf monotherapy 2.5 mg/kg every 3 weeks [29].

The study is being conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines following approval by ethics committees and institutional review boards at each study site. All patients have provided written informed consent for participation.

Patient population

This master protocol study will enroll approximately 85 patients per substudy across both the DE and CE phases. In the DE phase, up to ten patients will be enrolled per investigational combination treatment dose level and more than one dose level may be evaluated. Upon identification of the RP2D for each combination and achievement of the feasibility criteria at interim analysis, the CE phase will open for enrollment. In the CE phase, at least 35 patients will be randomized to each combination substudy and to the shared belamaf monotherapy control group. Patients in the DE or CE phase will continue on treatment until disease progression, death, start of new anticancer treatment, withdrawal of consent or end of study.

Key inclusion criteria are age ≥18 years, histologically or cytologically confirmed MM (defined by the International Myeloma Working Group criteria) [41], exposure to ≥3 prior lines of therapy (consisting of an immunomodulatory agent, a PI and an anti-CD38 mAb), Eastern Cooperative Oncology Group performance score 0–2, and adequate hematologic and vital organ function (Supplementary Table 1). Previous anti-BCMA targeted therapy will be allowed, except prior belamaf at any time or CAR T-cell therapy within 3 months of screening.

Key exclusion criteria include current corneal epithelial disease (except mild punctate keratopathy), current unstable liver or biliary disease, or other malignancies (except those disease free for >2 years or curatively treated non-melanoma skin cancer) (Supplementary Table 1). Patients who previously received any mAbs within 30 days, systemic antimyeloma therapy or radiotherapy within 14 days, or plasmapheresis within 7 days of first dose of study drug, prior allogeneic transplant or major (except bone-stabilizing) surgery ≤30 days from screening will not be eligible. Additional inclusion/exclusion criteria may be applied dependent on the combination agent.

Objectives, end points & assessments

Dose exploration phase

The primary objective of the DE phase is to determine the safety and tolerability of belamaf in combination with other anticancer treatments in each substudy and to establish the RP2D for each combination treatment. The primary end points include dose-limiting toxicities (DLTs) observed during a 21-day DLT observation period. Adverse events (AEs) observed after completion of the DLT period for each patient will also be included in the overall safety assessment. The key secondary objective is to evaluate clinical efficacy per combination treatment using ORR (percentage of patients with partial response [PR] or better, according to International Myeloma Working Group response criteria) [41]. Other secondary end points will further explore drug concentrations and exposure, incidence of antidrug antibodies (ADAs) against intravenous biologic treatments, and further safety and tolerability, including ocular findings and other AEs of special interest (AESIs). Exploratory end points include PK and PD parameters for each agent, clinical benefit rate (defined as at least minimal response), PFS, DoR, time to response (TTR), OS, bone marrow minimal residual disease (MRD) status and various biomarkers and biologic characteristics at baseline and on treatment, including, but not limited to, BCMA expression in the bone marrow and serum soluble BCMA levels in circulation.

Cohort expansion phase

The primary objective of the CE phase is to assess the clinical activity of belamaf at the RP2D in combination with other anticancer treatments versus belamaf monotherapy, as measured by the ORR. Secondary efficacy end points, including PFS, DoR, TTR, OS and rates of PR, very good PR, complete response (CR), stringent CR and clinical benefit rate, will further assess the clinical activity of the combination treatment versus belamaf monotherapy. Other secondary end points will further characterize the safety of the combination treatment (AEs, ocular findings and other AESIs), evaluate plasma concentrations of belamaf and combination treatments in patients within each substudy, and evaluate incidence of ADAs against intravenous biologic treatments. Exploratory end points will include PK, PD, MRD status and candidate prognostic and predictive biomarkers driven by the biology of belamaf

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or the combination partner. Health-related QoL and patient-reported outcomes will also be assessed as part of the exploratory objectives, using telephone interviews and through measuring changes from baseline in ocular surface disease index [42], the Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events [43] and the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaires EORTC QLQ-C30 and EORTC-IL52 [44].

Belamaf statistical considerations

Statistical hypotheses

No formal statistical hypothesis will be tested in the DE phase. The CE phase will determine whether belamaf in combination with the selected therapies in each substudy improves the response rate compared with belamaf monotherapy. A combination treatment will be considered superior to belamaf monotherapy in ORR if the Bayesian posterior probability is at least 90% for the combination response rate being greater than belamaf monotherapy.

Analysis sets

The intent to treat (ITT) population will include all patients randomized to treatment, regardless of whether they received the study treatment. This ITT cohort will be the primary population for all efficacy end points in the CE phase. DE phase efficacy end points and all safety end points will be evaluated based on the safety population, which is defined as all patients who receive at least one dose of any component of the combination treatment. Patients will be analyzed according to the intervention received. The PK population will include patients from the safety population from whom at least one PK sample has been obtained and analyzed. The DLT-evaluable population will comprise a subset of patients in the DE phase who have received the first course of treatment containing both agents within a substudy and who either were followed up for 21 days or were withdrawn from the study within 21 days due to an AE that met the definition of a DLT.

Statistical analyses

The sample size (~85 patients per substudy) and operating characteristics were evaluated by simulations. The trial has been designed to detect an absolute difference between the treatment arms if the response rate for the combination therapy is 25% or more than that of belamaf monotherapy in the CE phase.

Patient disposition, treatment status, demographics and baseline characteristics, medical history, prior and concomitant therapies, and study treatment exposure will be summarized descriptively.

The primary analysis for all efficacy end points will be based on patients from both DE and CE phases according to dose combination levels and will be performed at 6 months after the last patient receives the first dose in CE for each substudy. ORR will be compared between combination treatment and monotherapy using a Bayesian approach [45]. There is no intention to compare response rates between combination treatments, and no multiplicity adjustment will be considered.

For all the time-to-event secondary end point analyses in the CE phase (TTR, DoR, PFS and OS), the median time-to-event with 95% CI will be estimated based on the Kaplan–Meier method. TTR and DoR will be analyzed at the primary analysis, whereas PFS and OS will be analyzed at the end of each substudy. The MRD negativity rate and corresponding 95% CI will be provided based on the ITT population.

A modified toxicity probability interval method will be used to guide dose escalation/de-escalation decisions in the DE phase [46]. An initial cohort of three patients will be recruited at a starting dose level. If the dose is considered to have an acceptable safety profile according to the modified toxicity probability interval principles, an additional $\leq$7 patients will be enrolled in this dose level.

All AEs will be reported from the start of treatment until 70 days after the last dose of study treatment. AESIs defined as corneal events, thrombocytopenia and infusion-related reactions will be summarized separately. Descriptive statistics of clinical laboratory test results and the health-related QoL changes from baseline at each scheduled visit will be presented.

As part of the PK analyses, concentration–time profiles will be plotted for the belamaf, total mAb, cysteine-mcMMAF and the combination partners. Data may be combined with statistics from other studies and may be analyzed using a population PK approach. If deemed appropriate and if data permit, exposure–response relationships between belamaf and/or combination partner exposure (e.g., dose, dose intensity, concentration, maximum concentration or area under the curve) and clinical activity and/or toxicity (e.g., response, corneal events) may be explored using population methods, separately for each combination as appropriate. If data permit,

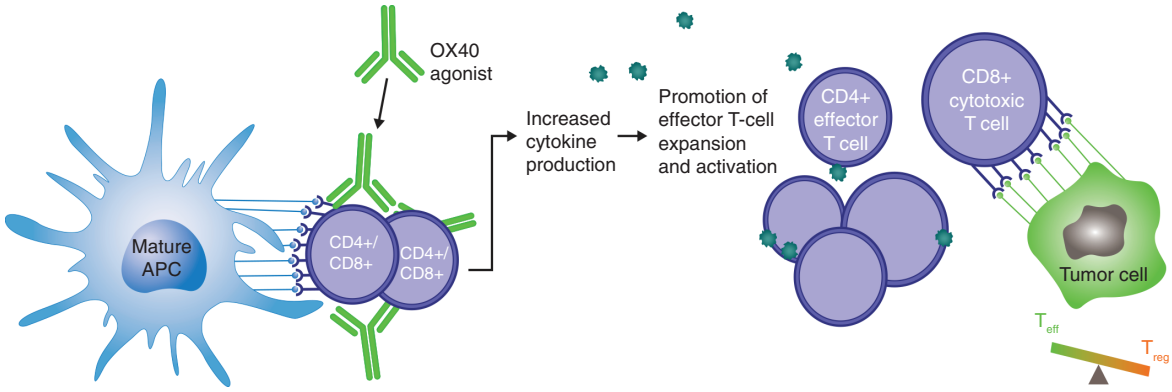

Figure 3. GSK3174998, a humanized wild-type IgG1 OX40 agonist mAb.
APC: Antigen-presenting cell; IgG: Immunoglobulin G; mAb: Monoclonal antibody; T_{eff}: Effector T cells; T_{reg}: Regulatory T cells.
Reproduced from [40].

the effects of covariates may be explored. ADAs will be analyzed for each assessment time point. During analyses of biomarkers and translational research, end points of interest will be summarized descriptively and/or graphically, as data permit.

Interim analysis

The interim analysis performed for each combination treatment at the end of the DE phase will evaluate safety (including DLTs, and AEs that are not DLTs), PK, PD and efficacy data, as data permit. Based on the results of the analysis, the RP2D for use in the CE phase will be selected. A minimum of two responders out of ten treated patients will be needed to initiate the CE phase of each substudy. The interim analysis will be performed when up to ten patients have been treated per dose level and have undergone three efficacy assessments, including one baseline and two postbaseline assessments, or have discontinued treatment due to confirmed progression, death or toxicity related to study therapy.

Evaluation of Grade 4 or higher treatment-related toxicity events will be performed per each ten patients treated with at least one cycle of belamaf and the combination agent. The combination arm with treatment-related Grade 4 or higher AEs that significantly (at one-sided alpha of 0.025) exceed those observed in the belamaf monotherapy arm will be considered to have unacceptable toxicity.

Substudies

Ongoing substudies of DREAMM-5 include combinations with agents selected based on scientific rationale and/or results of preclinical experiments in combination with belamaf. In addition to the master protocol as detailed above, each substudy may have specific patient inclusion and/or exclusion criteria, AESI, number of investigated dose levels and procedures for dose modifications.

Substudy 1: belamaf combination with GSK3174998, an OX40 agonist

OX40 is a co-stimulatory receptor and member of the TNF receptor superfamily. Expression of OX40 ligands on antigen-presenting cells (APCs), such as dendritic cells (DCs), B cells and macrophages, is induced upon activation by pathogen-associated molecular patterns or damage-associated molecular patterns released from dying cells [47,48]. 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) [49]. Preclinical and some early clinical studies have shown that OX40 agonists increase antitumor immunity and improve tumor-free survival [50]. Substudy 1 is investigating combinations of belamaf with GSK3174998. GSK3174998 is a humanized wild-type IgG1 OX40 agonistic mAb that binds to the co-stimulatory OX40 receptor expressed primarily on activated $CD4^+$ and $CD8^+$ T cells [51]. GSK3174998 has the potential to overcome immune resistance and enhance immune-mediated antitumor activity. This activity is anticipated to be further enhanced when combined with an agent causing ICD, such as belamaf. Belamaf inhibits microtubule polymerization, resulting in apoptosis, which is accompanied by release of key markers of ICD, potentially contributing to an adaptive immune response

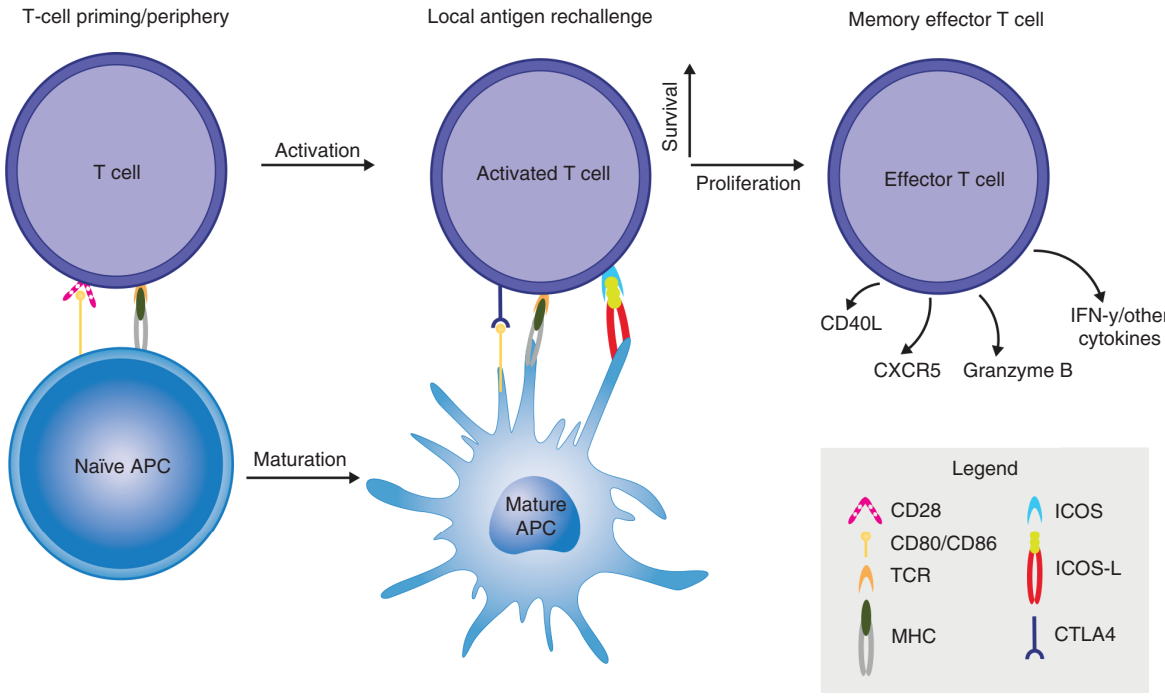

Figure 4. Feladilimab (GSK3359609), a T-cell activating IgG4 ICOS agonist mAb.
APC: Antigen-presenting cell; ICOS-L: ICOS ligand; IFN: Interferon; IgG: Immunoglobulin G; mAb: Monoclonal antibody; MHC: Major histocompatibility complex.
Reproduced from [58].

and immunologic memory [25]. A recent preclinical study demonstrated significantly higher antitumor activity and survival, and durable CRs with belamaf plus a mouse anti-OX40 surrogate antibody compared against each single agent. The observed antitumor activity was presumably due to the increased infiltration and activation of intratumor DCs, antigen-presenting T cells and induced hallmarks of ICD [25]. These data provided a rationale to evaluate the combination in this clinical trial.

Substudy 2: belamaf combination with feladilimab (GSK3359609), an ICOS agonist

ICOS is a co-stimulatory receptor and member of the CD28 superfamily. ICOS plays an important role in the proliferation, differentiation, survival, and function of T cells [52]. In preclinical studies, ICOS co-stimulation promoted antitumor activity [52–55]. Feladilimab is a humanized ICOS agonist IgG4 mAb selected for its nanomolar binding to and agonistic activity in ICOS-expressing $CD4^+$ and $CD8^+$ effector T cells. Feladilimab was designed and the fragment crystallizable region optimized to act as a true agonist to enhance T-cell function and enable antitumor responses without the depletion of ICOS-expressing cells (Figure 4) [56]. The unique mechanistic profile of feladilimab as an ICOS agonist allows investigation of the antitumor potential of targeting a T-cell co-stimulator alone and in combination with belamaf. Belamaf enhances antigen presentation through ICD, during which damage-associated molecular patterns released from the dying cells activate DCs [25,52]. When activated, DCs engulf dying cells presenting antigens, which may lead to priming of T cells and upregulation of ICOS on $CD4^+$ and $CD8^+$ T cells [25,57]. Therefore, combining belamaf with antitumor immune response-enhancing agents, such as feladilimab, could potentially offer enhanced antitumor activity due to complementary mechanisms of action. Preliminary data in animal models on the combination of feladilimab with belamaf revealed a trend of survival advantage over each monotherapy agent (unpublished data).

Substudy 3: belamaf combination with nirogacestat (PF-03084014), a gamma-secretase inhibitor

Nirogacestat is an oral, selective, small molecule, reversible, noncompetitive gamma-secretase inhibitor in clinical development for patients with desmoid tumors [59,60]. A Phase III study (NCT03785964) in desmoid tumors is ongoing. Gamma-secretase inhibitors were originally evaluated in neurologic diseases and more recently in cancer and rare tumors [61]. Gamma-secretases are intramembrane multi-subunit protease complexes [61] shown to cleave

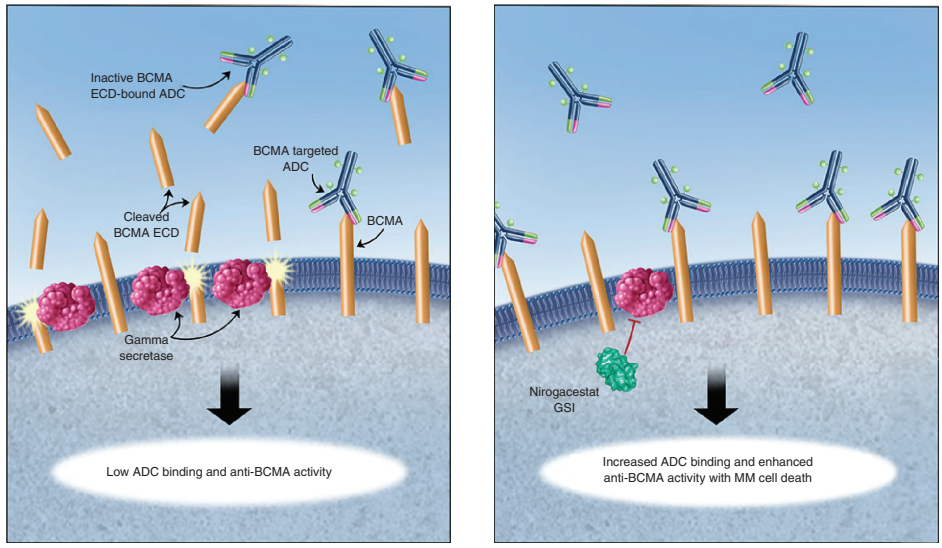

Figure 5. Mechanism of action of nirogacestat, a small molecule gamma-secretase inhibitor (PF-03084014), in combination with belamaf.
ADC: Antibody–drug conjugate; ECD: Extracellular domain (also refered to in this manuscript as soluble BCMA); GSI: Gamma-secretase inhibitor; MM: Multiple myeloma.
Reproduced from [65].

the extracellular domain of membrane-bound BCMA, releasing a soluble form (sBCMA) into circulation [62]. Inhibition of gamma-secretase activity increases cell-surface levels of BCMA and also reduces levels of sBCMA in circulation that may interfere with and limit efficacy of BCMA-directed therapy (Figure 5) [63]. Further, preclinical data in cell line models have shown that combining belamaf and nirogacestat increases cell-surface levels of BCMA in MM cell lines and enhances belamaf payload-mediated direct cell kill and ADCC activity *in vitro*, leading to a synergistic antitumor effect in MM cells, which provided the rationale to support clinical evaluation of this combination in RRMM [64].

Substudy 4: belamaf combination with dostarlimab (GSK4057190), an anti-PD-1 mAb

PD-1 is a transmembrane receptor, predominantly expressed on T cells, B cells, natural killer cells and other tumor-infiltrating lymphocytes [66]. PD-1 ligands (PD-L1 and PD-L2) are expressed by APCs and certain nonimmune cells, including tumor cells [66]. PD-1 and its ligands form an immune inhibitory checkpoint involved in T-cell activation and tolerance [66]. Binding of PD-L1 or PD-L2 to PD-1 inhibits lymphocyte activation and promotes immune tolerance to self-antigens to avoid tissue damage, but it also blocks the antitumor response of immune cells [66,67]. Tumors have been shown to utilize the PD-1 signaling pathway by upregulating PD-L1 expression to evade immune control and facilitate tumor progression [67–70]. Dostarlimab is a humanized anti-PD-1 IgG4 mAb that blocks interactions with PD-L1 and PD-L2 (Figure 6). Early clinical data with dostarlimab showed encouraging antitumor activity in patients with endometrial cancer [71]. Expression of PD-1 and its ligands has been reported in MM [72,73]. Studies investigating PD-1 inhibitors in combination with immunomodulatory drugs in patients with MM have not been successful. Therefore, the potential of PD-1 inhibitors in combination with other novel agents warrants further exploration in MM [74,75]. Combining belamaf with a PD-1 inhibitor has the potential to augment the antitumor response caused by belamaf-mediated ICD and ADCC and/or prevent tumor immune escape.

Discussion

Although significant improvements have been made in the treatment of MM, there is still an urgent unmet medical need for patients with RRMM. The vast majority of patients with MM will eventually relapse, and patients who have not responded to the current SoC treatments have a poor prognosis [76]. Patients who are refractory to multiple therapies, including PIs, immunomodulatory agents and/or anti-CD38 therapies have particularly poor outcomes and reduced OS [76,77]. Both Phase I and II studies have demonstrated that belamaf monotherapy

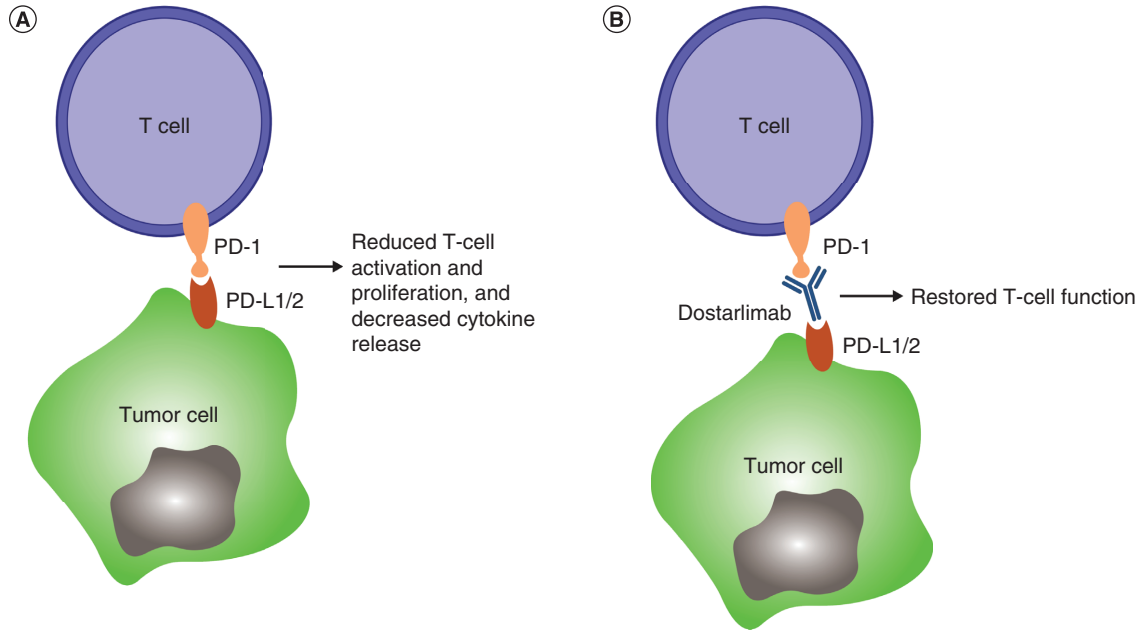

Figure 6. Dostarlimab (GSK4057190), a humanized IgG4 anti-PD-1 mAb. (A) Immune checkpoint in absence and **(B)** presence of dostarlimab.
IgG: Immunoglobulin G; mAb: Monoclonal antibody.
Reproduced from [40].

has clinically meaningful efficacy with a manageable safety profile in heavily pretreated patients with RRMM [27–29]. This manuscript describes the study design of the DREAMM-5 Phase I/II platform study, which evaluates the safety, tolerability and clinical activity of multiple novel belamaf-containing combinations in patients with RRMM. Initially, the DREAMM-5 study will evaluate belamaf in combination with an OX40 agonist mAb, an ICOS agonist mAb (feladilimab), a small molecule gamma-secretase inhibitor (nirogacestat), and an anti-PD-1 mAb (dostarlimab), compared with belamaf monotherapy, using a platform study design. Additional substudies may be incorporated based on emerging data.

Antibodies that target immune inhibitory checkpoints have been shown to reverse immune resistance in some tumor types [56,78]. Preclinical studies with mAbs that target OX40, ICOS and PD-1 have shown enhanced immune-mediated antitumor responses in certain clinical settings [53,56,79]. Furthermore, improved antitumor activity has been observed in combination with other agents, including other immune checkpoint antibodies [56,75,80].

Similarly, promising clinical responses and enhanced activity have been observed by combining gamma-secretase inhibitors and BCMA CAR T-cell therapy. Although BCMA is membrane-bound and predominantly expressed on plasma cells, recent studies have shown that gamma-secretases are able to cleave BCMA, releasing it into the circulation as a soluble protein, thereby reducing BCMA density on the surface of tumor cells and interfering with BCMA-targeting agent function [62]. The addition of the oral gamma-secretase inhibitor to increase membrane BCMA expression in order to increase the efficacy of CAR T-cell therapy and belamaf treatment (*in vitro*) has also been documented [64,81,82]. By increasing membrane-bound BCMA and decreasing sBCMA levels, nirogacestat in combination with belamaf could help optimize and/or enhance belamaf clinical efficacy and safety. Furthermore, higher levels of sBCMA are found in the blood serum of patients with monoclonal gammopathy of undetermined significance, smoldering MM and MM, compared with healthy individuals [83], and sBCMA levels correlate with disease burden, PFS and OS in patients with MM [84,85]. Therefore, there is a strong rationale to use sBCMA as a biomarker with potential prognostic and/or predictive value in MM and to monitor target engagement and disease status in the context of this trial.

Preclinical data for belamaf in combination with other therapies demonstrate significantly enhanced direct and indirect anti-MM activity. This suggests that the clinical efficacy seen with belamaf monotherapy in clinical studies of patients with RRMM may be further improved when coupled with the complementary mechanism of action of a rational combination treatment.

The DREAMM-5 study is a platform trial, which will allow multiple belamaf-based combinations to be evaluated contemporaneously. 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 trial based on the results from an algorithm [18,86]. The advantage of platform trials is that they can be structured to evaluate different treatments in parallel, compared with a shared control [18,19], with all treatment arms sharing a common statistical analysis plan with predefined criteria [19].

Simulation studies have shown that platform trial designs offer substantial advantages compared with traditional two-arm studies [19]. The main differences between standard clinical trials and platform trials are the use of a master protocol over a stand-alone protocol and the adaptive, rather than fixed, design features [87]. Platform trials offer the ability to evaluate multiple interventions concurrently as well as sequentially, whether the multiple therapies are experimental, SoC or a combination of the two [87]. This type of trial design also offers the ability to flexibly evaluate biomarkers of interest for the treatment paradigms, paving the way for personalized medicine with the identification of patient subpopulations most likely to benefit, or conversely, to incur AEs from a given treatment.

Platform trials have been used successfully to study a variety of different diseases and agents and may be especially valuable in RRMM where multiple options exist and mechanisms of resistance are increasingly complex [19,88]. The DREAMM-5 study is the first to investigate the efficacy of novel belamaf-containing treatment combinations in RRMM in this innovative Phase I/II trial design setup and will hopefully translate into an effective treatment platform to meaningfully improve patient outcomes [89].

Executive summary

- Multiple myeloma (MM) is a malignancy of plasma cells and is the second most common blood cancer after non-Hodgkin lymphoma. The incidence of MM is rising, and despite responses to currently available therapies, it remains an incurable disease; patients become increasingly refractory to successive treatments, with progressively shorter periods of remission between relapses.
- Therefore, there is a need in relapsed/refractory MM (RRMM) for treatments with novel mechanisms of action that may be combined to optimize responses and overcome resistance.
- Belantamab mafodotin (belamaf, GSK2857916) is a first-in-class BCMA-targeted antibody–drug conjugate approved as a single agent for the treatment of patients with RRMM who have received ≥4 prior lines of therapy.
- The DREAMM-5 study is a global randomized, open-label, Phase I/II platform trial in which the efficacy and safety of belamaf-containing novel treatment combinations will be evaluated in separate substudies versus a belamaf monotherapy arm.
- Patients who have been randomized to substudies will be allocated by a predetermined algorithm to substudies: belamaf plus GSK3174998 (OX40 agonist monoclonal antibody [mAb]); belamaf plus feladilimab (GSK3359609; an ICOS mAb); belamaf plus nirogacestat (a small molecule gamma-secretase inhibitor: PF-03084014); belamaf plus dostarlimab (an anti-PD-1 mAb), or a shared belamaf monotherapy control arm.
- Each substudy consists of a dose exploration (DE) and then a cohort expansion (CE) phase, with approximately 85 patients enrolled per substudy across both phases (including ≤10 patients per dose level in the DE phase and ≤35 patients in the CE phase).
- The primary end points are dose-limiting toxicities and adverse events in the DE phase and overall response rate in the CE phase.
- Other end points common to both phases include response per International Myeloma Working Group criteria and further efficacy measures (adverse events of special interest, ocular findings on ophthalmic examination), pharmacokinetics, incidence of antidrug antibodies, pharmacodynamics, biomarkers and minimal residual disease status; additional end points in the CE phase are health-related quality of life and patient-reported outcomes.
- The DREAMM-5 study will evaluate potential synergy of belamaf combined with novel agents and inform on new combinations for patients with RRMM.

Supplementary data

An infographic accompanies this paper and is included at the end of the references section in the PDF version. To view or download this infographic and the supplementary data which accompanies this article, please click here: https://www.futuremedicine.com/doi/full/10.2217/fon-2020-1269

Acknowledgments

The authors thanked J Opalinska and K Luptakova for their contribution to initiating the DREAMM-5 study.

Financial & competing interests disclosure

Study funded by GSK (study 208887); belamaf drug linker technology licensed from Seagen Inc.; belamaf monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa; nirogacestat gamma-secretase inhibitor produced by and used in collaboration with SpringWorks Therapeutics, Inc. AK Nooka received consultancy fees from Adaptive Technologies, Amgen, Bristol-Myers Squibb (BMS), Celgene, GlaxoSmithKline (GSK), Janssen, Karyopharm, Oncopeptides, Sanofi and Takeda; research support from Amgen, Janssen, and Takeda; and personal fees from GSK. K Weisel received consultancy fees and honoraria from Adaptive, Amgen, BMS, Celgene, GSK, Janssen, Karyopharm, Sanofi and Takeda; and research funding from Amgen, Celgene, Janssen and Sanofi. Nvd Donk received research support from Amgen, BMS, Celgene, Janssen and Novartis; and serves in advisory boards for Amgen, Bayer, BMS, Celgene, Janssen, Novartis, Roche, Servier and Takeda. D Routledge received consultancy fees from Celgene and Sandoz; and honoraria from Amgen, BMS, Celgene and Sandoz. PR Otero received honoraria from Amgen, Celgene, GSK, Janssen, Kite Pharma and Sanofi; and consulting fees from AbbVie, Celgene, GSK, Janssen, Kite Pharma, Oncopeptides, Sanofi and Takeda. K Song received consultancy fees from Amgen, Celgene and Takeda; research funding from Celgene and Janssen; and honoraria from Amgen, Celgene, Janssen, Otsuka and Takeda. H Quach received consultancy fees from Amgen, Celgene, GSK, Janssen and Karyopharm; research funding from Amgen, Celgene and Sanofi; and honoraria from Amgen, Celgene, GSK, Janssen and Karyopharm. N Callander received research funding from Cellectar. MC Minnema received funding from Celgene and honoraria from Amgen, Celgene, Gilead, Janssen and Servier. S Trudel received consultancy fees from Amgen, Celgene and GSK; research funding from Amgen, Celgene, Genentech, GSK and Janssen; and honoraria from Amgen, Celgene, Janssen, Karyopharm, Sanofi and Takeda. S Cheng and LM Smith are paid employees of SpringWorks Therapeutics (SWTX) and have SWTX stocks and shares. N Hareth has no conflicts of interest to declare. NA Jackson, CM Ahlers, E Im, G Ferron-Brady, M Brouch, RMd Oca, S Paul, B Holkova, I Gupta and BE Kremer are paid employees of GSK and have GSK stocks and shares. P Richardson has served on advisory committees for AbbVie, Celgene, GSK, Janssen, Karyopharm, Oncopeptides, Sanofi and Takeda; and has received research funding from Takeda, Celgene and BMS. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing support was provided by J Nikitorowicz-Buniak and MS d'Alcontres, of Fishawack Indicia Ltd, part of Fishawack Health, and funded by GSK.

Data sharing statement

GSK makes available anonymized individual participant data and associated documents from interventional clinical studies which evaluate medicines, upon approval of proposals submitted to www.clinicalstudydatarequest.com. To access data for other types of GSK sponsored research, for study documents without patient-level data and for clinical studies not listed, please submit an enquiry via the website.

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Belantamab Mafodotin in Combination With Novel Agents in Relapsed/Refractory Multiple Myeloma: DREAMM-5 Study Design

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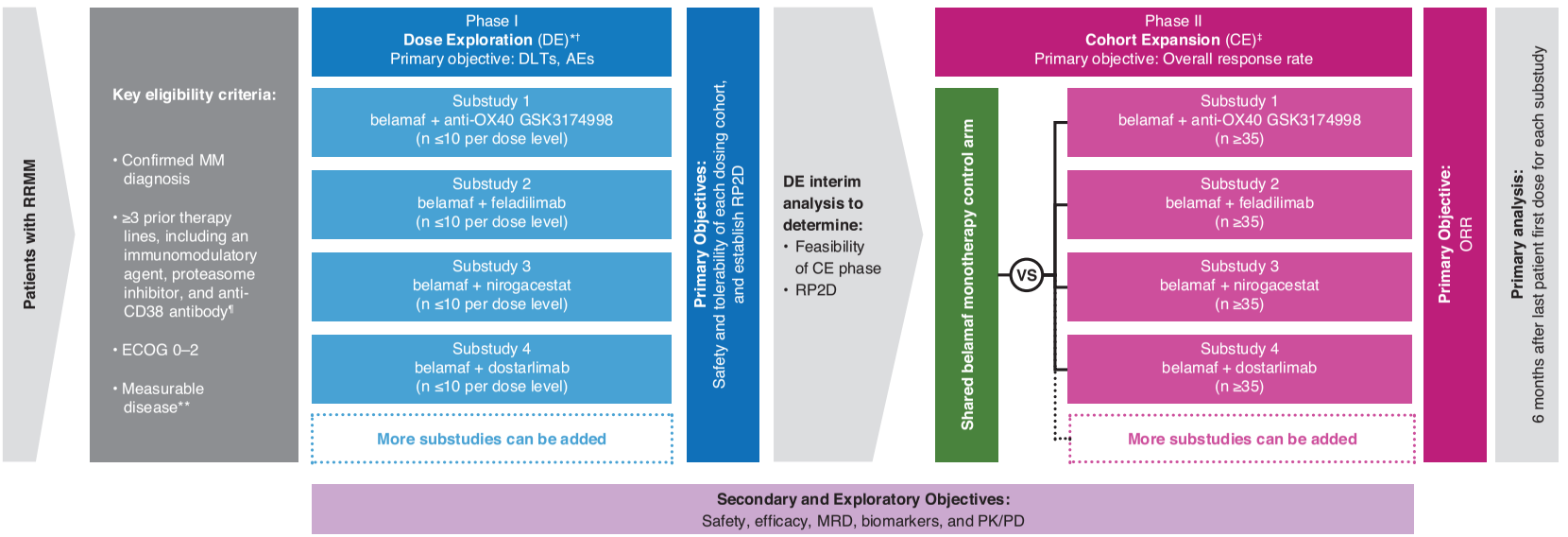
Flexible study design to evaluate the efficacy and safety of BCMA-targeting belantamab mafodotin (belamaf; BLENREP) in RRMM in combination with other anti-cancer agents with different MoAs



*Substudies 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 substudy or dose level is enrolling, allocation will be by pre-determined algorithm; ‡Participants in CE are stratified by substudy 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; BCMA: B-cell maturation antigen; CE: Cohort expansion; DE: Dose explorations; DLT: Dose-limiting toxicity; dostarlimab, a programmed cell death receptor-1 blocker; DREAMM: DRiving Excellence in Approaches to Multiple Myeloma; ECOG: Eastern Cooperative Oncology Group; feladilimab, an inducible T-cell co-stimulatory agonist; MoA: Mechanism of action; MRD: Minimal residual disease; nirogacestat, a gamma-secretase inhibitor; ORR: Overall response rate; PD: Pharmacodynamics; PK: Pharmacokinetics; RP2D: Recommended Phase 2 dose; RRMM: Relapsed/refractory multiple myeloma.

10.2217/fon-2020-1269

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Nooka, AK; Weisel, K; van de Donk, NWCJ; Routledge, D; Otero, PR; Song, K; Quach, H; Callander, N; Minnema, MC; Trudel, S; Jackson, NA; Ahlers, CM; Im, E; Cheng, S; Smith, L; Hareth, N; Ferron-Brady, G; Brouch, M; de Oca, RM; Paul, S; Holkova, B; Gupta, I; Kremer, BE; Richardson, P

Title:
Belantamab mafodotin in combination with novel agents in relapsed/refractory multiple myeloma: DREAMM-5 study design

Date:
2021-03-08

Citation:
Nooka, A. K., Weisel, K., van de Donk, N. W. C. J., Routledge, D., Otero, P. R., Song, K., Quach, H., Callander, N., Minnema, M. C., Trudel, S., Jackson, N. A., Ahlers, C. M., Im, E., Cheng, S., Smith, L., Hareth, N., Ferron-Brady, G., Brouch, M., de Oca, R. M. ,... Richardson, P. (2021). Belantamab mafodotin in combination with novel agents in relapsed/refractory multiple myeloma: DREAMM-5 study design. FUTURE ONCOLOGY, 17 (16), pp.1987-2003. https://doi.org/10.2217/fon-2020-1269.

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