Exploring Alternative Dosing Regimens of Single-Agent Belantamab Mafodotin on Safety and Efficacy in Patients With Relapsed or Refractory Multiple Myeloma: DREAMM-14

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Background

Belantamab mafodotin is a first-in-class, monomethyl auristatin F (MMAF)-containing, B-cell maturation antigen (BCMA)-directed antibody-drug conjugate approved in the US and EU for adult patients with relapsed/refractory multiple myeloma (RRMM).[1,2]

In the pivotal Phase 2 DREAMM-2 study (NCT03525678), single-agent belantamab mafodotin (2.5 mg/kg administered intravenously every 3 weeks [Q3W]) demonstrated deep (≥VGPR=58% of responders) and durable responses with a manageable safety profile in triple-class refractory adult patients with RRMM.[3,4]

At 13 months of follow-up in DREAMM-2, overall response rate was 32%.[4]

- The median estimated duration of response and overall survival were 11 (4.2–not reached) months and 13.7 (9.9–not reached) months, respectively.[4]

Keratopathy and ocular symptoms (including changes in best-corrected visual acuity [BCVA]) are a known effect of MMAF and have been observed in patients treated with belantamab mafodotin; these events may be managed with dose reductions or delays.[3–6]

- Keratopathy (including superficial punctate keratopathy and/or microcyst-like epithelial changes; observed in 27% of patients in the 2.5 mg/kg cohort in DREAMM-2),[3] decline in BCVA, and patient-reported adverse events (AEs) (eg, blurred vision or dry eye) have been observed with belantamab mafodotin in DREAMM-2.[3–6]

Studies exploring alternative dosing regimens and combination strategies have shown promising preliminary results,[7,8] and retrospective analyses of DREAMM-2 data show a correlation between BCVA changes, patient-reported outcomes, and keratopathy[9] that suggests ocular symptoms and severity of visual acuity changes may be a surrogate for keratopathy severity. These findings highlight that alternative dosing approaches or monitoring may be useful to reduce rates or severity of keratopathy and ocular symptoms without compromising efficacy.

Aims

To investigate whether an improved overall benefit/risk profile for single-agent belantamab mafodotin can be achieved by modifying the belantamab mafodotin dose, schedule, or both (Arms B–D) relative to the approved dosing regimen (2.5 mg/kg Q3W, Arm A) in an effort to reduce the risk of keratopathy and ocular symptoms (including BCVA changes) without a clinically meaningful decrease in efficacy.

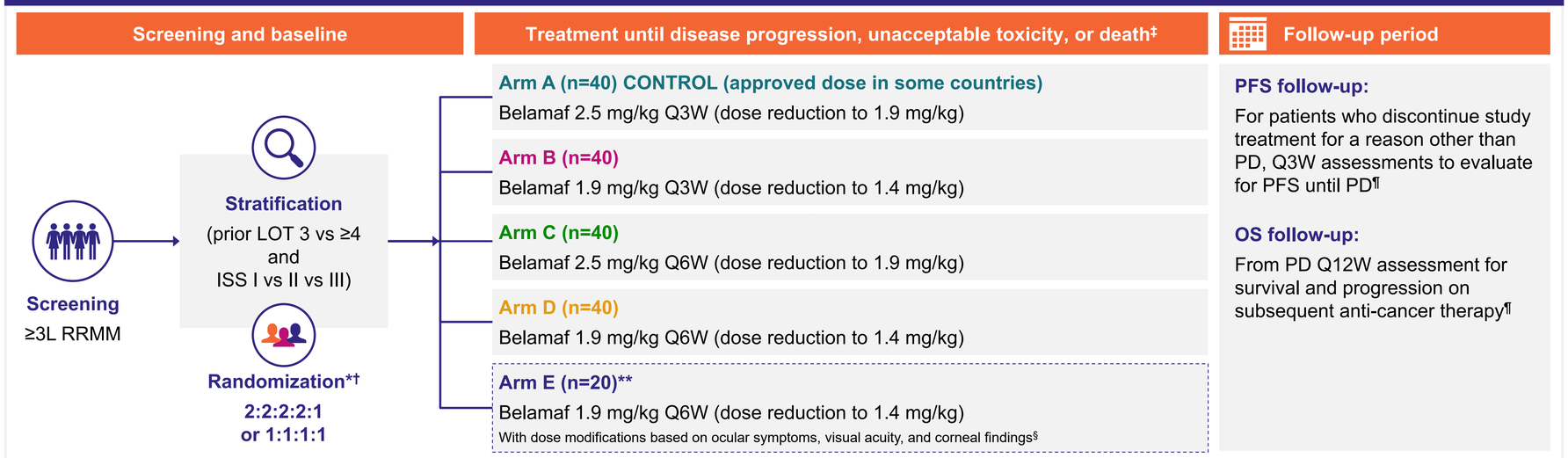
To explore whether alternative ocular monitoring could guide dose modifications (Arm E).

Methods

Study design

DREAMM-14 (NCT05064358) is a Phase 2, 5-arm, randomized, parallel, open-label multicenter study evaluating efficacy and safety of belantamab mafodotin at different doses and administration schedules (**Figure 1**) in a patient population with RRMM similar to that of DREAMM-2.

Figure 1. DREAMM-14 study design



ISS, International Staging System; LOT, line of therapy; OS overall survival; OSDI, Ocular Surface Disease Index; PD, progressive disease; PFS, progression-free survival; QXW, every X weeks; RRMM, relapsed/refractory multiple myeloma.
*2:2:2:2:1 into Arms A to E in parallel at sites participating in optional Arm E; 1:1:1:1 into Arms A to D in parallel at sites not participating in optional Arm E. †Planned target of 20% of participants who have received 3 prior LOTs. ‡The dose of study treatment will be based on patient's body weight calculated at baseline and may be modified to manage toxicities according to protocol guidelines. §Allowed dose modifications for keratopathy and ocular symptoms based on patient-reported symptoms using the Ocular Surface Disease Index (OSDI) and oncology staff assessment of visual acuity (Snellen chart or equivalent) and corneal examination findings. ¶Follow-up will occur until withdrawal of consent, loss to follow-up, end of study, or death. The end of study is defined as the time when all patients die, progress, withdraw consent, or have been followed up by a minimum of 15 months from the time the last participant receives their first dose of study treatment.
**Site participation in Arm E is optional and based on site interest and ability.

Objective and endpoints

Table 1. Key DREAMM-14 study objectives and endpoints

Primary objective and endpoint	**To examine the ocular AEs associated with single-agent belantamab mafodotin in DREAMM-14 using alternative dosing regimens in Arms B to D compared to Arm A** • Incidence rate of Grade ≥2 ocular AEs according to a modified keratopathy and visual acuity (KVA) scale				
Secondary objectives and endpoints	**To further evaluate ocular safety and tolerability of alternative dosing regimens** • Cumulative event rate of ocular AEs to Week 16* • Incidence rate of ocular AEs by grade* • Exposure-adjusted incidence rate of ocular AEs by grade* • Median duration of dose delay • Percentage of participants requiring dose modifications and treatment discontinuation due to ocular AEs* • Duration of ocular AEs* • Percentage of time on study with ocular AEs* • Change in BCVA	**To evaluate the efficacy of alternative dosing regimens** • ORR, defined as the percentage of participants with a confirmed PR or better • Percentage of participants with a confirmed VGPR or better • DoR • TTP • PFS • OS	**To evaluate the overall safety and tolerability of alternative dosing regimens** • Instance of AEs (including ocular AEs)† and changes in laboratory parameters • % of participants requiring dose modifications and treatment discontinuation due to any AEs†	**To assess the PK of belantamab mafodotin using alternative dosing regimens** • Plasma belantamab mafodotin PK parameters	**To assess ADA of belantamab mafodotin using alternative dosing regimens** • Incidence and titers of ADAs and total mAb plasma concentration at each ADA time point
Exploratory objectives and endpoints	**To determine the feasibility of dosing modifications based on ocular symptoms, visual acuity changes, and corneal findings compared to dosing based on KVA (Arm E only)** • The incidence of keratopathy (all grades), visual acuity changes, ocular symptoms, and related impacts based on OSDI in the symptom-based dose modification arm will be assessed and also compared to the selected standard dose modification control arm (Arm A)				

ADA, anti-drug antibody; AE, adverse event; BCVA; best corrected vision acuity; CTCAE, Common Terminology Criteria for Adverse Events; DoR, duration of response; KVA, keratopathy visual acuity scale; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; OSDI, Ocular Surface Disease Index; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; TTP, time to progression; VGPR, very good partial response.
*Assessed by KVA scale. †Assessed by CTCAE v5.0.

Patient population

Key patients' eligibility criteria are presented in **Table 2**.

Table 2. Key DREAMM-14 patient inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • ECOG Performance Status 0–2 • Confirmed MM (IMWG criteria)[10] • Measurable disease (according to serum and/or urine M-protein and/or serum free light chain levels) • Prior SCT or SCT ineligible • 3 or more prior lines of therapy (≥3), including an anti-CD38 antibody, and refractory status to an immunomodulatory agent and a proteosome inhibitor • History of autologous SCT (if >100 days prior to initiation of study treatment and no active infections) • All prior treatment-related toxicities Grade ≤1 at the time of enrollment (CTCAE criteria)* • Life expectancy of ≥6 months • Informed consent	• Symptomatic amyloidosis, active POEMS syndrome or active plasma cell leukemia • Current corneal epithelial disease, except nonconfluent superficial punctate keratitis • Malignancies other than the MM (>2 years disease-free, except for curatively treated non-melanoma skin cancer may be enrolled without a 2-year restriction • Evidence of cardiovascular risk • Active infection requiring antibiotic, antiviral, or antifungal therapy • Known human immunodeficiency virus (HIV) infection, unless the criteria in protocol can be met • Pregnancy or lactation • HBV or HCV infection unless certain parameters are met† • Prior exposure to anti-BCMA therapy or antibody-drug conjugate • Prior treatment with a monoclonal antibody ≤30 days before the first dose of study treatment • Presence of active renal condition, mucosal or internal bleeding, cirrhosis or current unstable liver or biliary disease • Ongoing Grade ≥2 peripheral neuropathy or neuropathic pain

BCMA, B-cell maturation antigen; CD38, cluster of differentiation 38; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IMWG, International Myeloma Working Group, MM, multiple myeloma; POEMS, polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes; SCT, stem cell transplant.
*Except for alopecia and Grade 2 peripheral neuropathy. †A patient with HBV or HCV may be included if they have a negative HCV RNA test result and have undergone successful antiviral therapy (usually 8 weeks duration), followed by a negative HCV RNA test result after a washout period of ≥4 weeks.

Current status

The duration of this study will be approximately 28 months.

The study is currently recruiting patients.

Disclosures

MH has carried out advisory or expert activity for BMS, Curio Science LLC, and GSK, and received scientific research funding from Amgen, Daiichi Sankyo, and GSK. **DK** is an employee at Calm Water Therapeutics LLC, has carried out advisory or expert activity for Accelerator, GSK, and Triphase, and owns shares/stocks/funds in Eyeon Therapeutics, Inc. **PG, AM, WE, TL, RCJ, JB, LE, ES**, and **JO** are employees of and hold stocks and shares in GSK. **JB** also holds stocks and shares in Novartis and Adaptimmune. **RCJ** also hold stocks and shares in Novartis and Alcon. **AM** also holds stocks and shares in Alcon and AstraZeneca.

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