Phase I/II, Open-label, 2-Arm Study to Evaluate Safety, Tolerability and Clinical Activity of Belantamab Mafodotin (GSK2857916) in Combination With 2 Standard-of-Care (SoC) Regimens in Relapsed/Refractory Multiple Myeloma – DREAMM 6

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Costa LJ[1], Quach H[2], Stockerl-Goldstein K[3], Augustson B[4], Ferron-Brady G[5], Chopra B[6], Moore A[5], Hudson S[6], Zhou J[5], Bragulat V[5], Talekar MK[5], Frey S[5], Opalinska JB[5]

[1]University of Alabama at Birmingham, Birmingham, AL, USA; [2]University of Melbourne, St. Vincent's Hospital, Melbourne, Australia; [3]Washington University in St. Louis, St. Louis, MO, USA; [4]QE II Medical Centre, Nedlands, Australia; [5]GSK, Collegeville, PA, USA; [6]GSK, Uxbridge, Middlesex, UK

Introduction

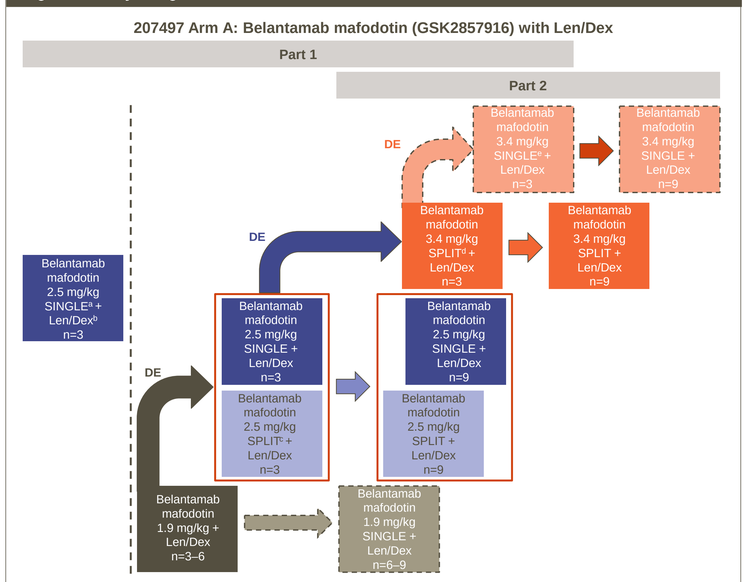
- B-cell maturation antigen (BCMA) is a validated therapeutic target in multiple myeloma (MM).
- Belantamab mafodotin (GSK2857916) is a humanized IgG1-type anti-BCMA monoclonal antibody conjugated to monomethyl auristatin-F via a protease-resistant maleimidocaproyl linker and produced in an afucosylated form to enhance antibody-dependent cellular cytotoxicity.
- In the first-in-human study BMA117159 (NCT02064387), Belantamab mafodotin was well tolerated and showed promising clinical activity as monotherapy in heavily pretreated patients with MM. The overall response rate was 60% with a mPFS of 12 months (95% CI: 3.1–not estimable).[1]
- Belantamab mafodotin, in combination with standard-of-care (SoC) therapies, could further improve outcomes for patients with relapsed/refractory MM (RRMM).
- DREAMM 6 (NCT03544281) is a 2-part, Phase I/II, open-label, dose-escalation and expansion study in patients with RRMM evaluating the safety, tolerability, and preliminary clinical activity of Belantamab mafodotin in combination with two approved SoC regimens in two parallel, independent arms: Arm A, Belantamab mafodotin plus lenalidomide/dexamethasone (Len/Dex) on a 28-day cycle, or Arm B, Belantamab mafodotin plus bortezomib/dexamethasone (Bor/Dex) on a 21-day cycle.

Methods

Study design

- DREAMM 6 is a 2-part study:
  - Part 1 (dose-escalation phase) will evaluate the safety, tolerability, and pharmacokinetics (PK) of up to 3 doses (1.9, 2.5, and 3.4 mg/kg) and up to 2 dosing schedules of Belantamab mafodotin in combination with Len/Dex on a 28-day cycle (Arm A), or Bor/Dex on a 21-day cycle (Arm B).
  - Part 2 (expansion phase) will further evaluate the safety, preliminary clinical activity, and PK of Belantamab mafodotin in combination with Len/Dex or Bor/Dex at the dose levels and dosing schedules defined in Part 1, and recommend the dose and schedule for further investigation.
- A protocol amendment was implemented based on emerging safety data from Arm A and evaluation of additional dose levels and dosing schedules.
- An alternative dosing schedule with a split dose approach for Belantamab mafodotin will be investigated as indicated in **Figure 1**. The first dose to be investigated in Arm A in Part 1 will be 1.9 mg/kg (dose level –1).

Figure 1. Study design



Arm A: combination therapy continued until disease progression, death, intolerable toxicity, consent withdrawn. Cohorts followed-up for PFS and OS.

Arm B: combination therapy continued for up to 8 cycles. Belantamab mafodotin further continued until disease progression, death, intolerable toxicity, consent withdrawn. Cohorts followed-up for PFS and OS.

[a]Belantamab mafodotin SINGLE = full assigned dose of Belantamab mafodotin administered on Day 1 of any 28-day (Arm A) or 21-day (Arm B) cycle.

[b]Lenalidomide (25 mg on Days 1–21) + dexamethasone (40 mg on Days 1, 8, 15, and 22) of any 28-day cycle.

[c]Belantamab mafodotin 2.5 mg/kg SPLIT = 1.25 mg/kg on Day 1 and 1.25 mg/kg on Day 8 of any 28-day (Arm A) or 21-day (Arm B) cycle.

[d]Belantamab mafodotin 3.4 mg/kg SPLIT = 1.7 mg/kg on Day 1 and 1.7 mg/kg on Day 8 of any 28-day (Arm A) or 21-day (Arm B) cycle.

[e]Belantamab mafodotin 3.4 mg SINGLE = may be evaluated based on risk/benefit assessment of Belantamab mafodotin 3.4 mg/kg SPLIT.

[f]Bortezomib (1.3 mg/m^2 on Days 1, 4, 8, and 11) + dexamethasone (20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12) of any 21-day cycle.

DE, dose escalation; OS, overall survival; PFS, progression-free survival.

- A modified Toxicity Probability Interval design[2] will guide dose escalation and expansion (Part 2) of the cohort at the given dose of Belantamab mafodotin in each arm for Part 1.
- Safety data from all enrolled participants will be monitored.
- The observed number of participants permanently discontinuing study treatment within the first 2 cycles due to an adverse event related to Belantamab mafodotin will be compared against defined safety stopping rules; enrollment may stop for a given dose/higher dose level(s) or dosing schedule(s) if the safety stopping rules are met.
- Patients will undergo an ocular examination prior to dosing. If there are no corneal signs, after dose 4 exam of Belanatmab mafodotin treatment, the examinations may be decreased to once every 12 weeks.
  - Corneal events will be managed through prophylaxis with steroid eyedrops. Preservative-free artificial tears must be administered in each eye at least 4–8 times daily beginning on Day 1 until end of treatment.
- Subjects in Arm A will continue combination treatment until progression, intolerable toxicity, consent withdrawal, or death.
- Subjects in Arm B will receive up to 8 cycles of Belantamab mafodotin in combination with Bor/Dex and then continue Belantamab mafodotin monotherapy until progression, intolerance, consent withdrawal, or death.

Patient population

- Key inclusion and exclusion criteria are shown in **Table 1**. Adult subjects with RRMM previously treated with ≥1 prior line of therapy who have undergone autologous stem cell transplant or are transplant-ineligible, and who have documented disease progression during or after their most recent therapy, will be enrolled.
- Part 1: n≤33 evaluable for dose-limiting toxicity (n≤21 in Arm A and n≤12 in Arm B).
- Part 2: n≤90 (n≤45 in Arm A and n≤45 in Arm B).
- Disease progression will be assessed using the International Myeloma Working Group response criteria.[3]

Study objectives and endpoints

- The planned primary and secondary objectives and endpoints are listed in **Table 2**.

Table 1. Key inclusion and exclusion criteria

Key inclusion criteria

All of the following criteria must apply:

- Male or female, aged ≥18 years
- Confirmed diagnosis of MM as defined by the IMWG criteria[4]
- ECOG performance status of 0 to 1 (Arm A) or 0 to 2 (Arm B)
- Prior autologous stem cell transplant, or transplant-ineligible
- Previously treated with ≥1 prior line of MM therapy and must have documented disease progression during or after their most recent therapy according to IMWG criteria[4]
- Measurable disease
- Prior autologous stem cell transplant is allowed if:
  - >100 days prior to study enrollment
  - No active infection present
- Prior treatment-related toxicities resolved to Grade ≤1
- Adequate organ system function

Key exclusion criteria

- Systemic anti-myeloma therapy within 14 days, or plasmapheresis within 7 days
- Prior treatment with a monoclonal antibody within 30 days
- Prior allogenic stem cell transplant
- Major surgery within the last 4 weeks
- Active renal condition, liver disease, biliary disease, infection, or bleeding
- Any serious and/or unstable pre-existing medical or psychiatric disorder or other conditions (including laboratory abnormalities) that could interfere with participant's safety, obtaining informed consent, or compliance to the study procedures
- Previous or concurrent invasive malignancies other than MM, unless medically stable for ≥2 years and the participant is not receiving active therapy for this disease, other than hormonal therapy (participants with curatively treated non-melanoma skin cancer are allowed without a 2-year restriction)
- Cardiovascular risk, including: QTcF interval >480 msec; evidence of current clinically significant untreated arrhythmias; history of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within 3 months of screening; NYHA Class III or IV heart failure; uncontrolled hypertension
- Known immediate or delayed hypersensitivity reaction or idiosyncratic reaction to drugs chemically related to Belantamab mafodotin or components of the study treatment
- Pregnant or lactating female
- Known HIV infection, positive for HBsAg or HBcAb, or HCV
- Corneal disease except for mild punctuate keratopathy

Additional exclusion criteria: Arm A

- Unable to tolerate antithrombotic prophylaxis
- Had discontinued prior treatment with lenalidomide due to intolerable adverse events

Additional exclusion criteria: Arm B

- Unacceptable adverse effects and/or ongoing Grade ≥2 peripheral neuropathy or neuropathic pain from previous bortezomib treatment
- Intolerance or contraindications to antiviral prophylaxis

ECOG, Eastern Cooperative Oncology Group; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IMWG, International Myeloma Working Group; NYHA, New York Heart Association; QTcF, QT interval corrected by Fridericia's formula.

Table 2. Primary and secondary objectives and endpoints

Objectives	Endpoints
Primary	
Dose-escalation	
• Determine safety and tolerability of Belantamab mafodotin in combination with either Len/Dex (Arm A) or Bor/Dex (Arm B) to establish a recommended dose range and schedule to evaluate in Part 2	• Number (%) of participants with DLTs • Number (%) of participants with AEs, changes in clinical signs and laboratory parameters
Dose-escalation and expansion	
• Select the dose(s) and dosing schedule for further investigation based on safety, tolerability, and clinical activity of Belantamab mafodotin plus either Len/Dex (Arm A) or Bor/Dex (Arm B)	• Comprehensive determination based on safety, AEs/SAEs, and ORR
Dose expansion	
• Determine preliminary clinical activity of Belantamab mafodotin in either Len/Dex (Arm A) or Bor/Dex (Arm B)	• ORR defined as % of participants achieving ≥PR (IMWG Uniform Response Criteria for MM[3])
Secondary: Dose escalation and expansion	
• Evaluate PK profile of Belantamab mafodotin when administered in combination with Len/Dex (Arm A) or Bor/Dex (Arm B)	• Belantamab mafodotin PK parameters, as data permit
• Evaluate PK profile of Len when administered with Belantamab mafodotin and Dex	• Len PK parameters in Cycle 1, as data permit
• Evaluate PK profile of Bor when administered with Belantamab mafodotin and Dex	• Bor PK parameters in Cycle 1, as data permit
• Assess ADAs against Belantamab mafodotin	• Incidence and titers of ADAs against Belantamab mafodotin pre-dose in Cycle 1 and selected subsequent cycles
• Evaluate the effect and tolerability of Belantamab mafodotin in combination with Len/Dex (Arm A) or Bor/Dex (Arm B) on symptomatic AEs	• Changes from baseline in symptoms and related impacts as measured by OSDI, NEI-VFQ-25, and PRO CTCAE
• Further characterize safety of Belantamab mafodotin administered with Len/Dex (Arm A) or Bor/Dex (Arm B)	• Incidence of AEs, including SAEs and AEs of special interest (corneal events, thrombocytopenia, and infusion-related reactions) • Ocular findings on ophthalmic examination
• Evaluate the effect of Belantamab mafodotin in combination with Len/Dex (Arm A) or Bor/Dex (Arm B) on HRQoL	• Changes from baseline in HRQoL as measured by the EORTC QLQ-C30 AND QLQ-MY20

ADA, anti-drug antibody; AE, adverse event; Bor, bortezomib; Dex, dexamethasone; DLT, dose-limiting toxicity; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; Len, lenalidomide; HRQoL, health-related quality of life NEI-VFQ-25, National Eye Institute Visual Functioning Questionnaire; ORR, overall response rate; OSDI, ocular surface disease-specific instrument; PR, partial response; PRO CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; SAE, serious adverse event.

Current status and conclusions

- Recruitment started in October 2018 and is ongoing; as of 16 May 2019, 3 patients have been enrolled in Arm A and 9 patients in Arm B. Enrollment into Arm A was temporarily paused after 2 subjects died due to neutropenia with concomitant infections. Both cases were confounded, but increased safety monitoring has been implemented via amendment. Enrollment to Arm A is expected to resume by July 2019; Arm B is continuing to enroll per protocol.
- DREAMM 6 will establish the safety, tolerability and PK profiles of Belantamab mafodotin plus Len/Dex or Bor/Dex, and provide recommended dose(s) for evaluation of Belantamab mafodotin in combination with SoC in subsequent comparative trials in patients with RRMM.

References

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Disclosures

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