Therapeutic Dose Selection for Belantamab Mafodotin, a BCMA-Targeting Agent, in Patients with Relapsed/Refractory Multiple Myeloma (RRMM): Application of Population Pharmacokinetics (PopPK) and Exposure-Response Analyses

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Disclosures

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Belantamab mafodotin (Belamaf; GSK2857916) is a first-in-class BCMA-targeting immunoconjugate\(^1\) being developed as a treatment option for patients with heavily pre-treated RRMM

This ADC is comprised of a humanized afucosylated anti-BCMA monoclonal antibody conjugated to a cytotoxic payload MMAF by a protease-resistant mc linker\(^1\)

- BCMA is a cell membrane receptor that is expressed on all malignant plasma cells and is essential for their proliferation and survival\(^2\)
- Belamaf binds to BCMA and eliminates MM cells by a multimodal mechanism of action, including, in part, delivery of MMAF to MM cells (Figure)\(^1\)
- In both Phase I (DREAMM-1; NCT02064387) and Phase II (DREAMM-2; NCT03525678) studies, single-agent belamaf demonstrated deep and durable clinical responses with a manageable safety profile in patients with heavily pre-treated RRMM\(^1,3,4\)
  - DREAMM-1: belamaf 0.03–4.6 mg/kg IV Q3W\(^3,4\)
  - DREAMM-2: belamaf doses 2.5 or 3.4 mg/kg IV Q3W\(^1\)

This analysis assessed PopPK of belamaf and cys-mcMMAF and exposure-response relationships for key efficacy and safety endpoints to support monotherapy dose selection
### Objectives and Methods

#### Objectives

- To characterize the popPK of **belamaf** and **cys-mcMMAF** in patients with RRMM and identify covariates of clinical interest
- To explore the relationship between exposure of belamaf and cys-mcMMAF and efficacy and AESI endpoints
- To support the **monotherapy dose recommendation**

#### Methods - Data

- PK samples from patients in DREAMM-1 (n=73)\(^2\) and DREAMM-2 (n=218)\(^1\) studies were analyzed for belamaf (ADC) and cys-mcMMAF concentrations
- **Efficacy** (IMWG criteria): ORR, PFS, TTR or TTBR and DoR
- **Safety** was monitored by CTCAE version 4.0 (DREAMM-1) and version 4.03 plus ocular exam scale (DREAMM-2). Grade ≥1, ≥2 and/or ≥3 ocular AE (KP, BV, DE) or ocular exam finding (OEF), grade ≥3 thrombocytopenia or neutropenia, and IRRs were captured

#### Methods – PopPK Modeling

- PopPK models were developed with a non-linear mixed-effect modelling approach using the NONMEM 7.3 software with the first order conditional estimation method with or without interaction (FOCE-I or FOCE)
- **Covariates of Interest**: demographics (gender, race, age, weight), organ function-related (albumin, ALT, AST, bilirubin, eGFR), disease-related (ISS stage, baseline sBCMA, IgG), and others (baseline platelet count, baseline neutrophil count, lyophile presentation, immunogenicity)
- Variables with the greatest improvement in objective function were selected step by step for inclusion in the full model (p≤0.01). A backward elimination process using a cutoff of p≤0.001 led to the final model
- Cycle 1 exposure (e.g. Cmax, Cavg, Ctau) were computed for belamaf and cys-mcMMAF and used in the exposure-response analyses

#### Methods – Exposure-Response Modeling

- Probability of response (PR or better) and occurrence of safety events were analyzed using **generalized linear models**
- Time-to-efficacy (PFS) or safety events were evaluated with **Kaplan-Meier** plot using quartile of exposure and covariates as well as via **Cox proportional hazard models** with baseline patient characteristics and Cycle 1 exposures as continuous variable

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Results – PopPK Model

Population PK models – Schema with Covariates

Belamaf PK model
CLt, V1, Q, V2

Typical patient
is a DREAMM-2 patient, a 65-year-old male weighing 75 kg and with mild renal impairment and normal liver function.
At baseline, sBCMA level was 100 ng/mL, IgG was 10 g/L, and albumin was 40 g/L.

Population PK models – Belamaf

• A two-compartment model with linear elimination with clearance (CLt) decreasing over time (time to 50% of maximal change: 50 days) described data well
• Systemic clearance: 0.92 L/day on Day 1 decreasing to 0.72 L/day over time; Steady-state volume of distribution: 10.8 L; Elimination half-life: 12 days on Day 1 increasing to 14 days over time

PopPK models – cys-mcMMAF

• A two-compartment model with linear elimination and decreasing cys-mcMMAF:mAb ratio after each dose (DARtad) described data well

In purple boxes, significant covariates with positive relationship or negative relationship.

Effect of Key Covariates on Exposure Parameters

Effect of Baseline sBCMA on Exposure Parameters

Effect of Baseline IgG on Exposure Parameters

Effect of Baseline Albumin on Exposure Parameters

Effect of Baseline Body Weight on Exposure Parameters

ALB, albumin; BW, body weight; Cavg, average concentration; CL, clearance; Cmax, peak concentration; Ctau, trough concentration; cys-mcMMAF, cysteine maleimidocaproyl monomethyl auristatin F; DAR, drug-antibody ratio; IgG, immunoglobulin G; IV, intravenous; mAb, monoclonal antibody; PK, pharmacokinetics; Q, intercompartmental clearance; sBCMA, soluble B-cell maturation antigen; t, represents a parameter varying over time; tad, represents a parameter varying over time after each dose; Vx, volume of distribution for each compartment.
Results – Exposure-Response

Exposure-Response Models – Schema with Covariates

- IV dose
- Belamaf Exposure Ctau
  - Baseline sBCMA
  - Cmax
- Efficacy
  - PoR, PFS
  - Baseline β2-microglobulin
  - IgG
- Safety
  - KP, BV, DE and OEF
  - History Dry Eye
  - Baseline Platelet
  - Baseline K
  - Baseline cys-mcMMAF
- Thrombocytopenia

In purple boxes, significant covariates with positive relationship or negative relationship.

Exposure-Response – Efficacy – DREAMM-2 only

- PoR and PFS were not related to drug exposure when accounting for the inverse relationship to baseline disease factors
- TTR but not TTBR was inversely related to belamaf Ctau

Exposure-Response – Safety – DREAMM-2 only

- Safety endpoints were strongly associated with exposure
- Higher belamaf Ctau was associated with probability of developing keratopathy and OEF and inversely correlated to time of onset
- Higher cys-mcMMAF Cmax and lower baseline platelet count were associated with increased probability of thrombocytopenia

In purple boxes, significant covariates with positive relationship or negative relationship.

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BV: Blurred vision; Cmax, peak concentration; Ctau, concentration on day 21; CTCAE, Common Terminology Criteria for Adverse Events; cys-mcMMAF, cysteine maleimidocaproyl monomethyl auristatin F; DE: Dry eye; IgG, immunoglobulin G; IRR, infusion-related reaction; KP: Keratopathy; OEF: ocular exam findings; ORR, overall response rate; PFS, progression-free survival; sBCMA, soluble BCMA; TTBR, time to best response; TTR, time to response.
Conclusions and Contact Information

• Belantamab mafodotin has dose-proportional PK with clearance decreasing over time. Its pharmacokinetics is influenced by patient characteristics, including IgG, sBCMA, albumin, and body weight.

• Increased probability of keratopathy and ocular exam findings and thrombocytopenia with higher exposure or dose was not associated with a commensurate improvement in efficacy in DREAMM-2.
  • Based on an integrated exposure-response analyses after accounting for patient characteristics.

• This analysis supports the recommendation of the 2.5 mg/kg IV Q3W dose for the use of single-agent belantamab mafodotin in patients with heavily pretreated RRMM.
  • Comparable efficacy of the 2.5 and 3.4 mg/kg dose observed in DREAMM-2

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