CT196

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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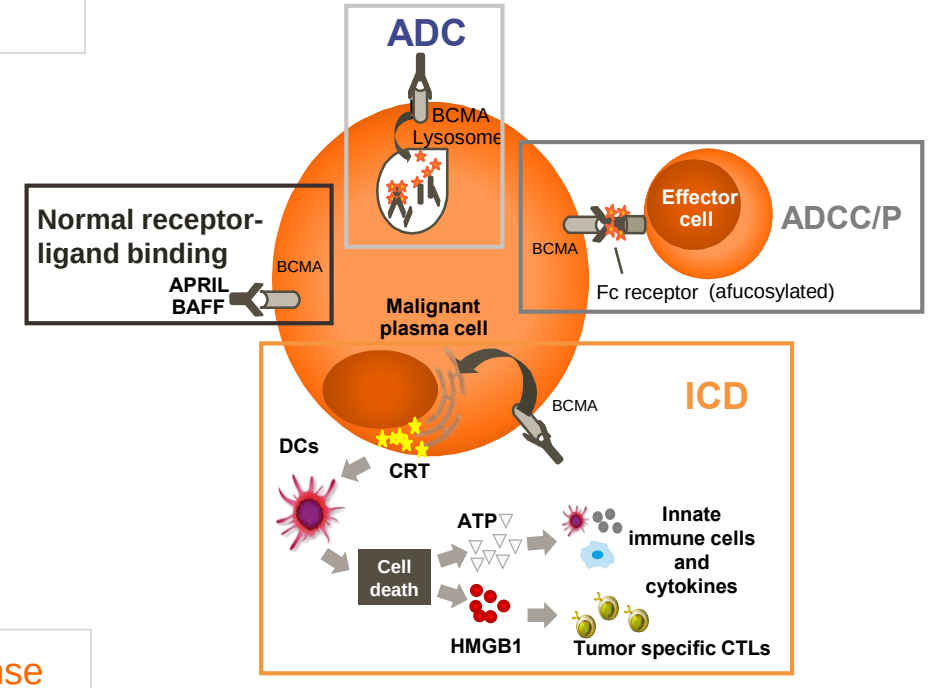
Background

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

ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; ADCC/P, antibody-dependent cellular cytotoxicity and phagocytosis; ATP, adenosine triphosphate; BCMA, B-cell maturation antigen; CRT, calreticulin; CTL, cytotoxic T-lymphocyte; cys-mcMMAF, cysteine maleimidocaproyl monomethyl auristatin F; DC, dendritic cells; Fc, fragment crystallizable; HMGB1, high-mobility group box 1; ICD, immunogenic cell death; IV, intravenous; mc, maleimidocaproyl; MM, multiple myeloma; MMAF, monomethyl auristatin F; popPK, population pharmacokinetics; Q3W, every 3 weeks; RRMM, relapsed or refractory multiple myeloma. 1. Lonial S et al. *Lancet Oncol,* 2020;21(2):207-21; 2. Tai YT. and Anderson KC. *Immunotherapy*, 2015;7(11):1187-99; 3. Trudel S et al. *Lancet Oncol* 2018;19:1641; 4. Trudel S et al. *Blood Cancer J* 2019;9(4):37.

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

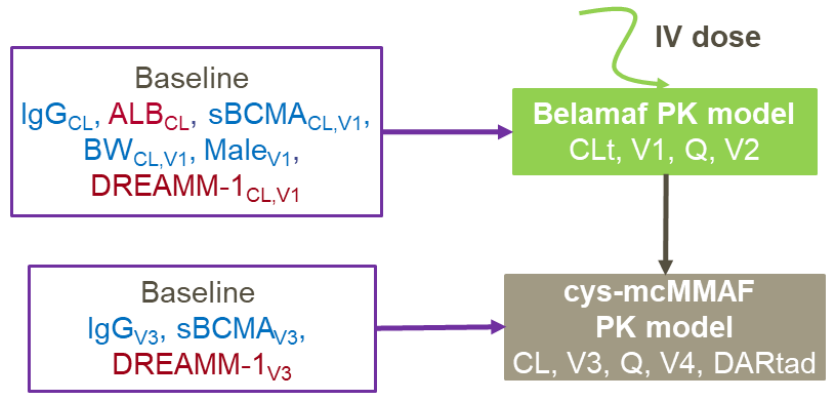
Methods – Exposure-Response Modeling

- 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

ADC, antibody-drug conjugate; AESI, adverse events of special interest; ALT, alanine transaminase; AST, aspartate aminotransferase; BCMA, B-cell maturation antigen; Belamaf: belantamab mafodotin; BV: Blurred Vision; Cavg, average serum concentration; Cmax, peak serum concentration; Ctau, trough concentration; CTCAE, Common Terminology Criteria for Adverse Events; cys-mcMMAF, cysteine maleimidocaproyl monomethyl auristatin F; DE: Dry Eye; eGFR, estimated glomerular filtration rate; FOCE, first order conditional estimation IgG, immunoglobulin G; IMWG, International Myeloma Working Group; IRR, infusion-related reaction; ISS, International Staging System; KP: keratopathy; MAb, monoclonal antibody; MMAF, monomethyl auristatin F; OEF, ocular exam findings; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetic; popPK, population pharmacokinetics; PPR, partial response; RRMM, relapsed/refractory multiple myeloma; sBCMA, soluble BCMA; TTBR, time to best response; TTR, time to response. 1. Lonial S et al. *Lancet Oncol* 2020;21:207-21; 2. Trudel S et al. *Lancet Oncol* 2018;19:1641.

Results – PopPK Model

Population PK models – Schema with Covariates



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

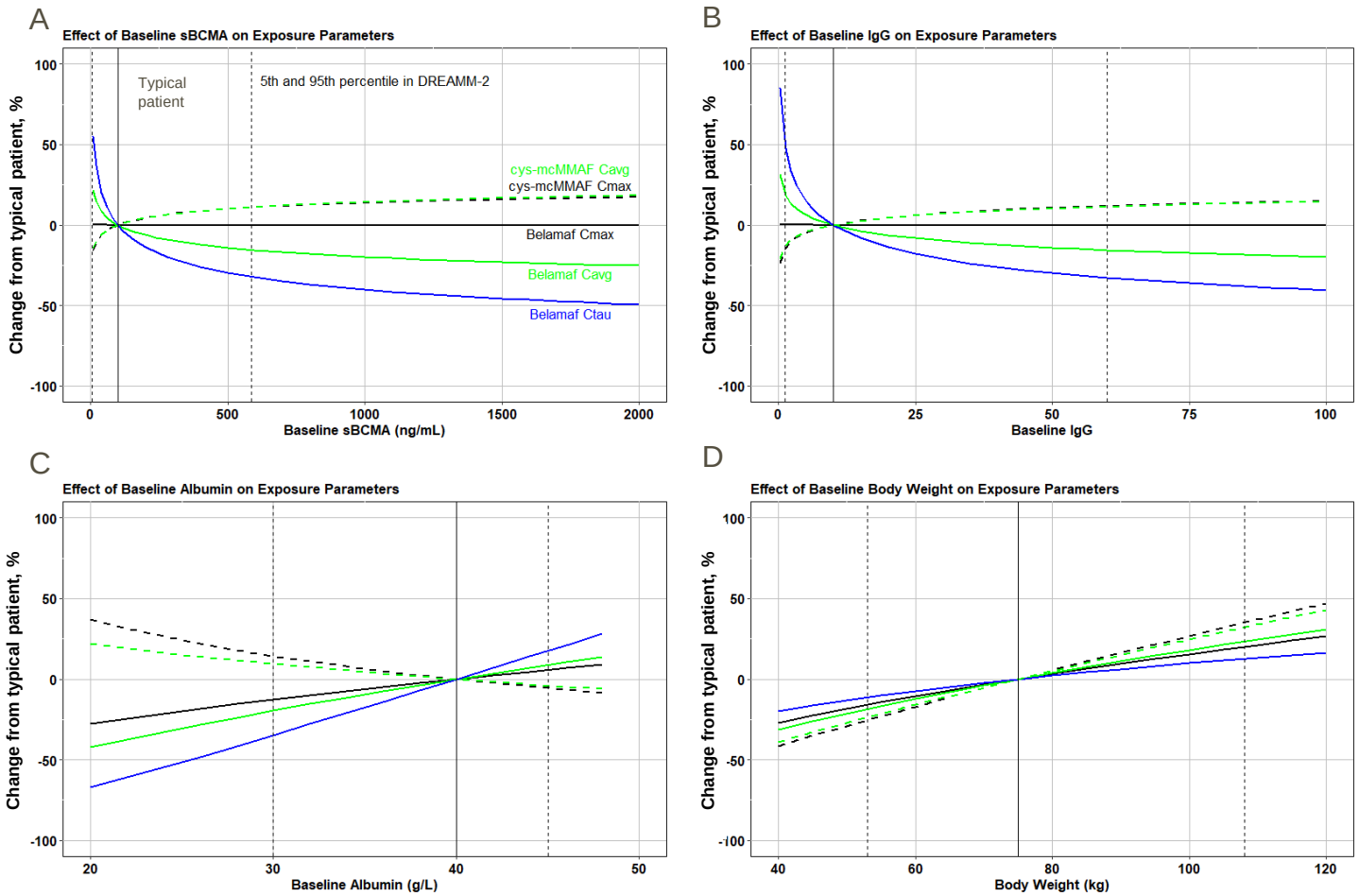
PopPK models – Belamaf

- 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

Effect of Key Covariates on Exposure Parameters

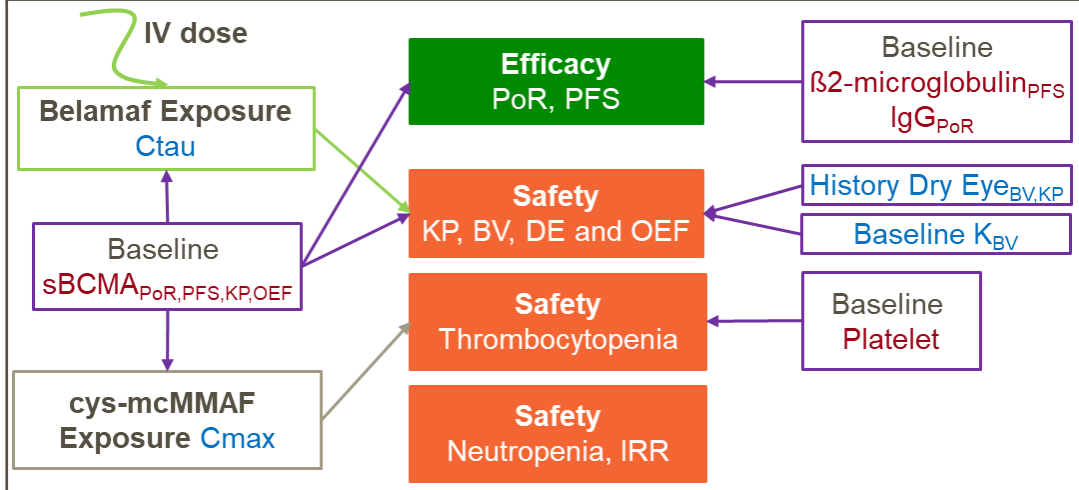


Typical patient is a DREAMM-2 patient, a 65-year-old male weighing 75 kg and with mild renal impairment and normal liver function. At baseline, sBCMA level was 100 ng/mL, IgG was 10 g/L, and albumin was 40 g/L.

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



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

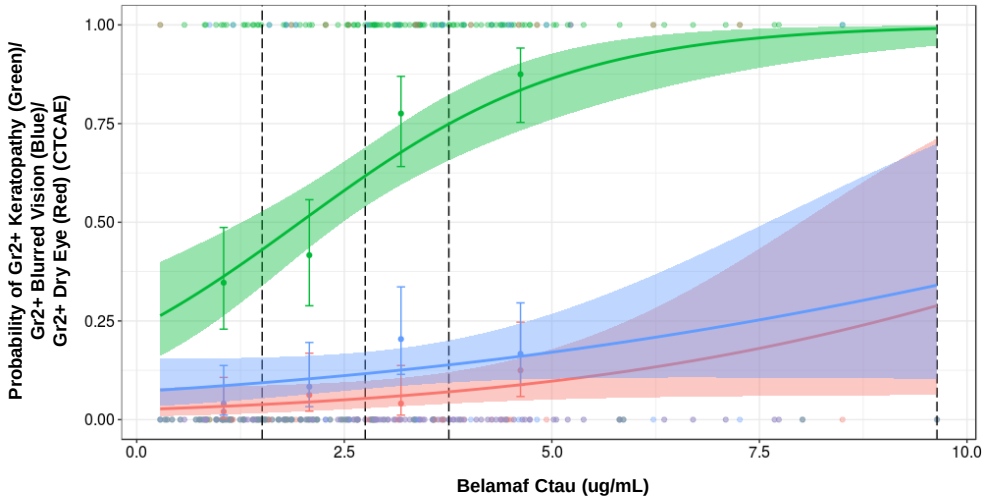
Exposure-Response – Efficacy – DREAMM-2 only

- **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

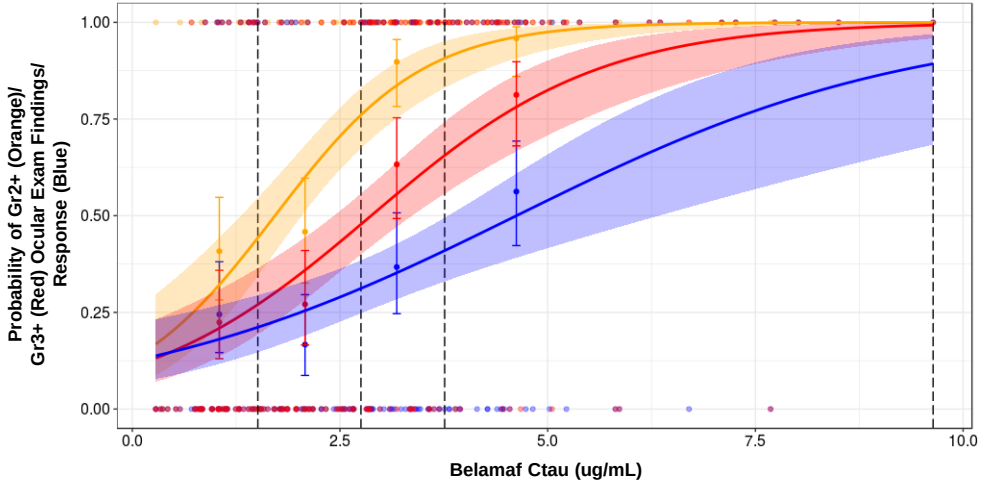
Exposure-Response – Safety – DREAMM-2 only

- **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**

A. Probability of Ocular AE vs Belamaf Ctau



B. Probability of Ocular Exam Finding and Efficacy vs Belamaf Ctau



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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IgG, immunoglobulin G; IV, intravenous; OEF, ocular exam findings; Q3W, every 3 weeks; RRMM, relapsed or refractory multiple myeloma; sBCMA, soluble B-cell maturation antigen.