B-cell Maturation Antigen Antibody-Drug Conjugate (ADC), Belantamab Mafodotin (GSK2857916), in Relapsed/Refractory Multiple Myeloma (RRMM): Final Safety, Efficacy and Pharmacokinetic (PK) Analyses From a Phase I Study

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Introduction

- Despite the introduction of immunomodulators and proteasome inhibitors (PI), outcomes remain poor for patients with relapsed/refractory multiple myeloma (RRMM).[1]
- The tumour necrosis superfamily cell-surface receptor, B-cell maturation antigen (BCMA), is expressed on MM cells[2,3] and associated with reduced survival.[3] Therefore, BCMA is a potential therapeutic target in MM.
- Belantamab mafodotin (GSK2857916) is a novel anti-BCMA monoclonal antibody (mAb) conjugated to the microtubule-disrupting agent monomethyl auristatin F via a protease-resistant maleimidocaproyl linker (mcMMAF); after cellular uptake of the antibody-drug conjugate (ADC), the active drug (cys-mcMMAF) is released.[4]
- Interim analysis of the first-in-human study of belantamab mafodotin in patients with RRMM (BMA117159; DREAMM1, NCT02064387) reported an overall response rate (ORR) of 60% (95% confidence interval [CI]: 42.1–76.1) at the recommended Phase 2 dose, and progression-free survival (PFS) of 7.9 months (95% CI: 3.1–not estimable).[5]

Aim

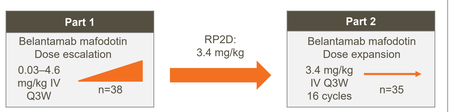
- Here we present the final analyses, a further 14 months after interim analysis, of the efficacy, safety, pharmacokinetic (PK) and biomarker findings from DREAMM-1.

Methods

Study design and patient population

- This open-label, 2-part Phase I study (BMA117159; NCT02064387) was conducted in 9 centres in the USA, Canada and UK in adults with MM and progressive disease after stem cell transplantation (or considered transplant-ineligible), alkylators, PIs and immunomodulators (**Figure 1**).
- In Part 1 (dose escalation), patients received GSK2857916 (0.03–4.6 mg/kg) via 1 h intravenous (IV) infusions once every 3 weeks (Q3W). In Part 2 (dose expansion), patients received the selected dose of 3.4 mg/kg Q3W for up to 16 cycles.
- An interim analysis was performed after ~4 months of follow-up (cut-off: 26 June 2017); the final analysis presented here was performed after ~18 months of follow-up (cut-off: 31 August 2018).

Figure 1. Study design



GSK2857916 FTIH: BMA117159

- Relapsed/refractory multiple myeloma
- GSK2857916 administered via IV infusion Q3W
- Part 1: Doses from 0.03 mg/kg up to 4.6 mg/kg examined (n=38)
- Part 2: 3.4 mg/kg chosen as RP2D (n=35)
- Primary endpoints: Safety, determine MTD and RP2D
- Secondary endpoints: Efficacy, PK, ADA
- Exploratory endpoints: Peripheral blood, serum and bone marrow samples collected at baseline and on-treatment for biomarker and PD analyses

ADA, anti-drug antibody; FTIH, first-time-in-human; IV, intravenous; MTD, maximum tolerated dose; PD, pharmacodynamic; PK, pharmacokinetic; Q3W, every 3 weeks; RP2D, recommended Phase 2 dose

Assessments

- Primary endpoints were safety, maximum tolerated dose and recommended Phase 2 dose.
- Secondary endpoints included clinical activity (percentage of patients achieving at least a partial response [overall response rate]), safety and tolerability via adverse event (AE) reporting and PK parameters.
- PK samples were collected during the first cycle in Part 1. PK parameters for the ADC, total mAb, and cys-mcMMAF were determined by noncompartmental analysis.
- MM biomarkers were assessed, including BCMA expression in bone marrow mononuclear cells and plasma cells by immunohistochemistry, and circulating free soluble BCMA (sBCMA) levels by immunoassay in serum.

Results

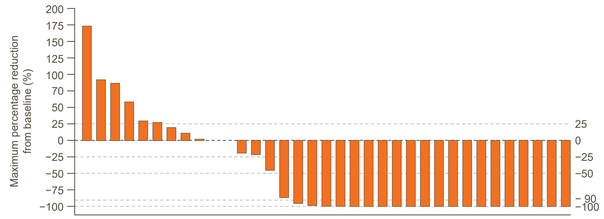
Patient population

- In Part 1, 38 patients were enrolled and analysed, with a mean (range) age of 59 (39–79) years.
- Thirty-five patients were enrolled in Part 2, with a mean (range) age of 61 (46–75) years; patients completed a median (range) of 12.5 (0.7–23.2) months of follow-up.

Safety and efficacy

- Safety and efficacy findings from the final analysis of Part 2 have been published.[6] In brief:
  - The most frequently reported AEs were corneal events (24/35; 69%), most commonly blurred vision (18/35; 51%), dry eye (13/35; 37%) and photophobia (10/35; 29%); the median duration (for patients with a resolution date [n=16]) was 35 days. The second-most frequent AE was thrombocytopenia (22/35; 63%). Treatment-related serious AEs were experienced by 7/35 (20%) patients, most commonly infusion-related reactions (2/35; 6.0%).[6]
  - The ORR was 60% (95% CI: 42.1–76.1). Median PFS was 12.0 months (95% CI: 3.1–not estimable), median duration of response was 14.3 months (95% CI: 10.6–not estimable) and median time to first response was 1.2 months (95% CI: 0.7–1.4) **(Figure 2)**.[6] A confirmed overall response was observed in 18/32 (56.3%; 95% CI: 37.7–73.6) patients refractory to both immunomodulators (IMiD) and PI, 15/21 (71.4%; 95% CI: 47.8–88.7) patients without prior daratumumab treatment and 5/13 (38.5%; 95% CI: 13.9–68.4) patients refractory to both IMiD and PI with prior daratumumab treatment.

Figure 2. Best Response to belantamab mafotodin*



Maximum percentage change from baseline in M-protein or free light chain. For patients with measurable serum M-protein, serum concentration is shown; for patients with urine M-protein measurements, urine concentrations are shown; and for patients with no available serum or urine M-protein measurements, free light-chain concentrations are shown.

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PK

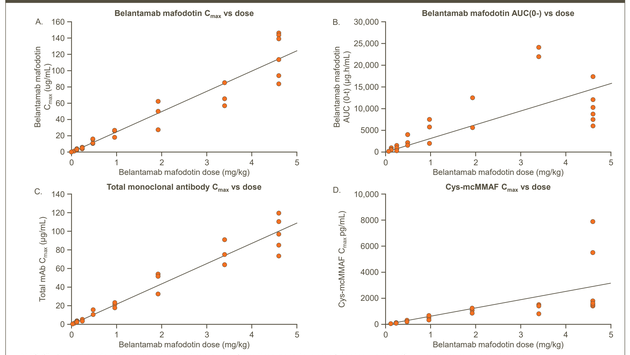
- Combining all dose levels in Part 1, geometric mean clearance of belantamab mafodotin was 18 mL/h, steady-state volume of distribution was 4.1 L, and half-life was 6.7 days (n=18) and the median time to maximum concentration (T_{max}) was 2.0 h (n=28). Similar PK parameter values were observed for total mAb (mAb with/without MMAF). The median T_{max} for cys-mcMMAF was 24.0 h (n=23); the geometric mean maximum concentration (C_{max}) at 3.4 mg/kg was 1200 pg/mL (n=3). PK parameters are summarised in **Table 1**.
  - The Q3W dosing regimen was selected based on preclinical data and on the projected half-life in humans
- Plasma exposures of belantamab mafodotin, total BCMA mAb and cys-mcMMAF appeared to increase proportionally with dose (**Figure 2**).

Table 1. Summary of PK parameters

Parameter	0.03 mg/kg (n=1)	0.06 mg/kg (n=1)	0.12 mg/kg (n=4)	0.24 mg/kg (n=4)	0.48 mg/kg (n=4)	0.96 mg/kg (n=3)	1.92 mg/kg (n=4)	2.5 mg/kg (n=8)	3.4 mg/kg (n=3)	4.6 mg/kg (n=6)	Total (n=38)
$AUC_{(0-t)}$ (µg.h/mL)	NC	200.5	633.4 (35)	729.4 (91)	2389[c] (51)	4448 (80)	9893[c] (52)	NC	23122[b] (7)	9739 (39)	NC
C_{max} (µg/mL)	0.43	1.32	2.96 (18)	4.55 (20)	11.9[c] (24)	23.1 (23)	43.8[c] (45)	NC	68.1 (21)	117 (24)	NC
T_{max} (h)	2.08	4.08	1.19 (1.00–2.00)	3.09 (2.00–8.78)	1.00[c] (1.00–4.00)	2.05 (2.00–2.08)	1.00[c] (0.50–24.00)	NC	6.92 (2.02–8.78)	1.56 (0.95–2.07)	2.00[f] (0.50–24.00)
C_{trough} (ng/mL)	NC	NC	382 (106)	1331[b] (44)	4307[a]	3720 (114)	11421[c] (36)	3727 (50)	28134[b] (36)	2301 (76)	NC
CL (mL/h)	NC	28.3	10.5 (59)	25.0[c] (89)	15.1[c] (75)	8.46[b] (27)	11.7[a]	NC	NC	38.8[d] (38)	17.9[e] (83)
V_{ss} (L)	NC	5239	2.90 (29)	4.29[c] (31)	4.39[c] (22)	3.22[b] (22)	5.16[a]	NC	NC	5.225[d] (19)	4.08[e] (32)
$t_{½}$ (days)	NC	5.26	7.84 (37)	4.91[c] (76)	8.27[c] (50)	11.0[b] (47)	12.9[a]	NC	NC	4.32[d] (17)	6.69[e] (54)

Data presented as geometric mean (%CVb), except T_{max} which is presented as median (minimum–maximum).
[a]n=1; [b]n=2; [c]n=3; [d]n=4; [e]n=18; [f]n=28.
$AUC_{(0-t)}$, area under the concentration-time curve from time zero to end of dosing period; C_{max}, maximum concentration; CL, clearance; C_{trough}, trough concentration; NC; not calculated; $t_{1/2}$, half life; T_{max}, time to C_{max}; V_{ss}, variation of biomass concentration

Figure 3. Plasma exposures of A) belantamab mafodotin (C_{max}), B) belantamab mafodotin (AUC), C) total anti-BCMA mAb (C_{max}) and D) cys-mcMMAF (C_{max}) by dose level (Part 1)

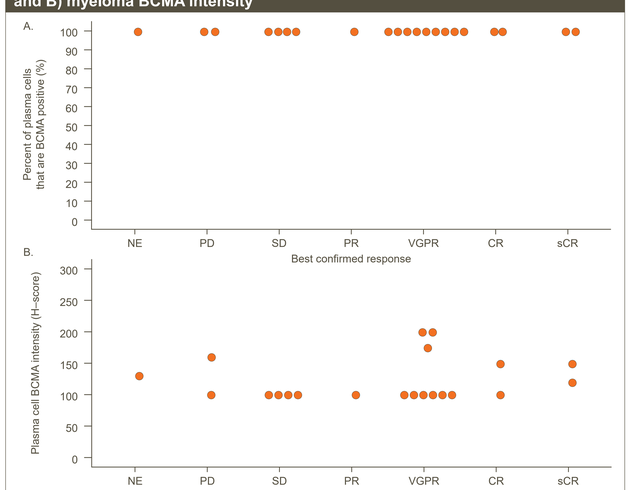


AUC (0-t), area under the concentration-time curve from time zero to end of dosing period; C_{max}, maximum concentration; mAb, monoclonal antibody.

Biomarkers

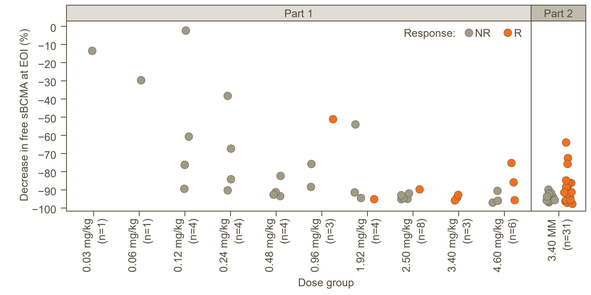
- 21/35 (60%) patients in Part 2 were positive for BCMA expression on MM cells at baseline (responding, n=21). No clear relationship was observed between level of baseline BCMA expression and response to treatment with belantamab mafodotin (**Figure 3**).
- Baseline BCMA was measured using immunohistochemistry of formalin-fixed paraffin-embedded bone marrow aspirates and was scored by a pathologist. No potential threshold was found.
- Belantamab mafodotin binds sBCMA in the circulation and is measured by reduced free sBCMA at Cycle 1 end of infusion. Greater than 90.0% reductions in free sBCMA were observed at doses ≥1.92 mg/kg with no relationship between response and free sBCMA reduction, indicating that sBCMA is saturated at higher doses of belantamab mafodotin (**Figure 4**). Free sBCMA concentrations increased over time after the initial decrease observed with belantamab mafodotin administration.
- Median baseline sBCMA was 45 ng/mL (7.19-262.46 ng/mL) in responders (n=20) and 89 ng/mL (19.32-1000 ng/mL) in non-responders (n=11). Response was achieved in patients with both low and high levels of baseline sBCMA, ranging from <10 ng/mL up to 262 ng/mL (**Figure 5**).

Figure 4. Baseline BCMA expression in A) Myeloma BCMA expression and B) myeloma BCMA intensity



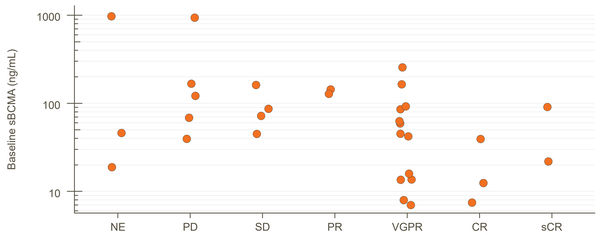
BMMC, bone marrow mononuclear cell; CR, complete response; NE, not evaluable; PC, plasma cell; PD, progressive disease; PR, partial response; SD, stable disease; sCR; stringent complete response; VGPR, very good partial response

Figure 5. Decrease in sBCMA at the end of belantamab mafodotin infusion



EOI, end of infusion; NR, no response; R, best response of partial response or better

Figure 6. Baseline sBCMA levels by response to treatment (Part 2)



CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response

Conclusions

- Belantamab mafodotin was well tolerated and demonstrated rapid deep and durable responses in heavily pre-treated patients with RRMM. With additional follow-up, more complete responses and considerably longer PFS was observed in the final analysis[6] compared with interim analysis.[5]
- The PK profile was characterised by slow clearance, a small volume of distribution and half-life of 6.7 days.
- No clear relationship between baseline surface BCMA expression level and patient response was identified.
- Corneal and thrombocytopenia events were consistent with the known toxicities of other MMAF-linked antibody-drug conjugates.[7]
- Belantamab mafodotin engaged sBCMA in a dose-dependent manner. Clinical responses were observed in patients across a wide range of baseline sBCMA levels.
- Further investigations are needed to understand the value of BCMA expression on MM cells and circulating free sBCMA as biomarkers for response to belantamab mafodotin.

References

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Disclosures

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