

# 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).<sup>1</sup>
- The tumour necrosis superfamily cell-surface receptor, B-cell maturation antigen (BCMA), is expressed on MM cells<sup>2,3</sup> and associated with reduced survival.<sup>3</sup> 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.<sup>4</sup>
- 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).<sup>5</sup>

## Aim

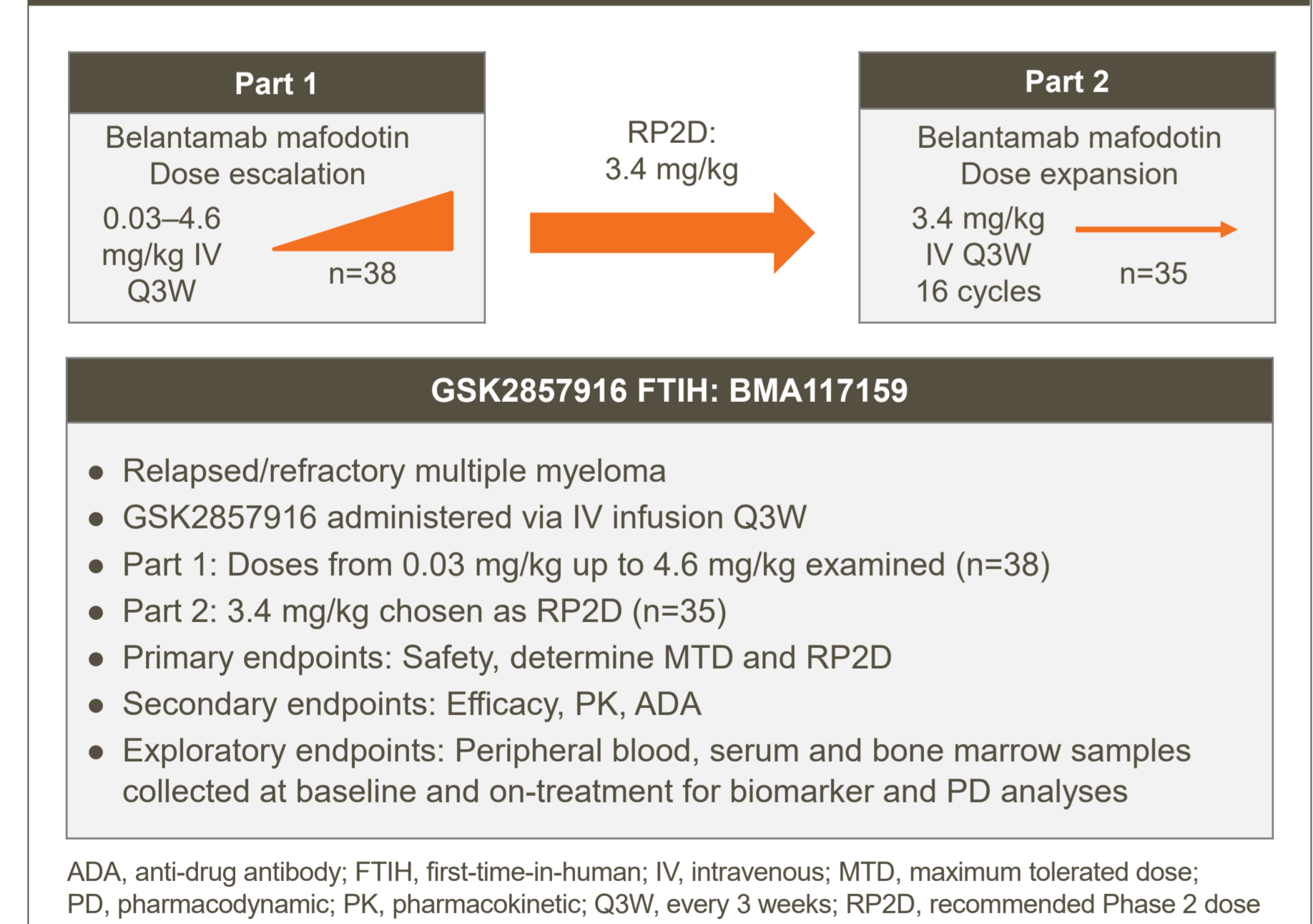
- Here we present the final analyses, a further 14 months after interim analysis, of the efficacy, safety, pharmacokinetic (PK) and biomarker findings from DREAMM-1.

## 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



### 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

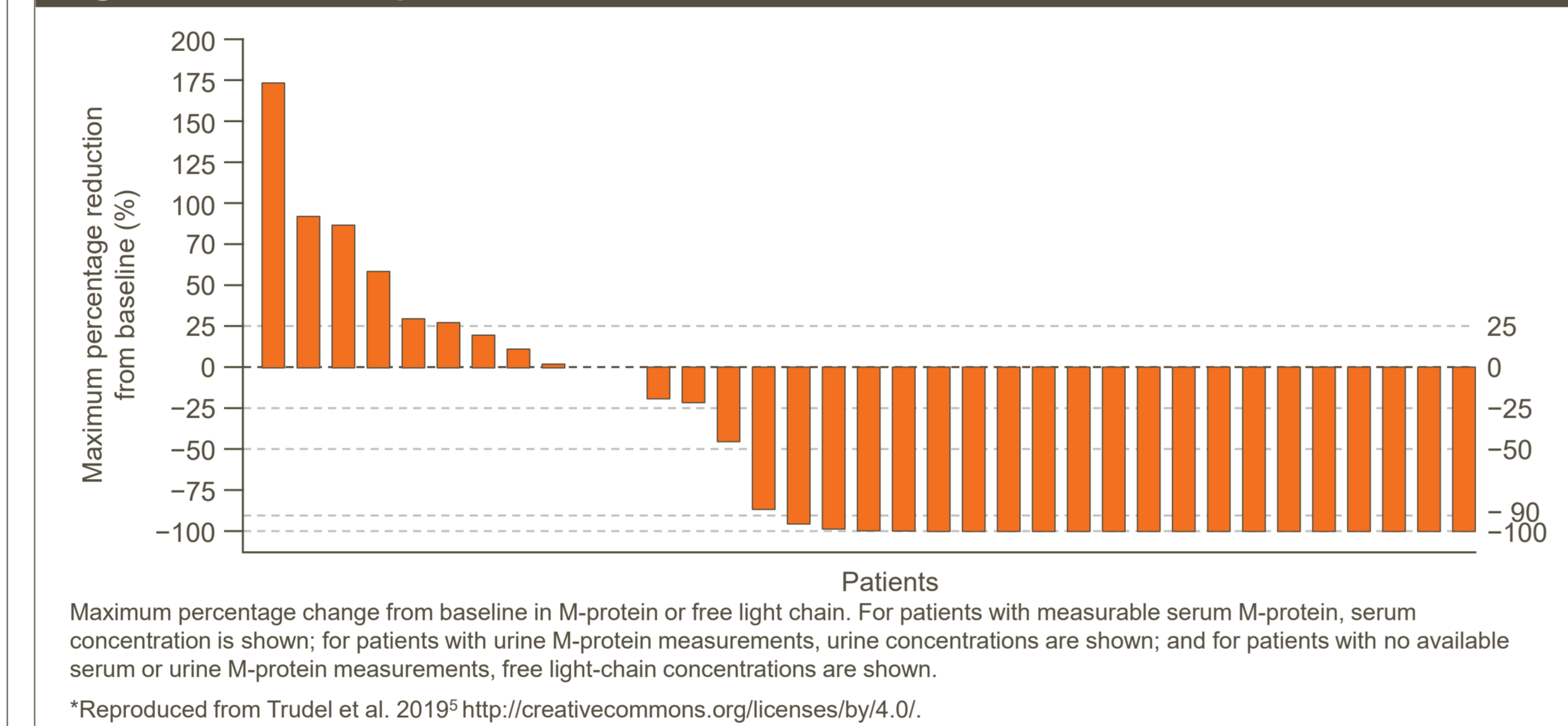
### Patient population

- 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.<sup>6</sup> 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%).<sup>6</sup>
  - 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).<sup>6</sup> 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 mafodotin\*



### 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

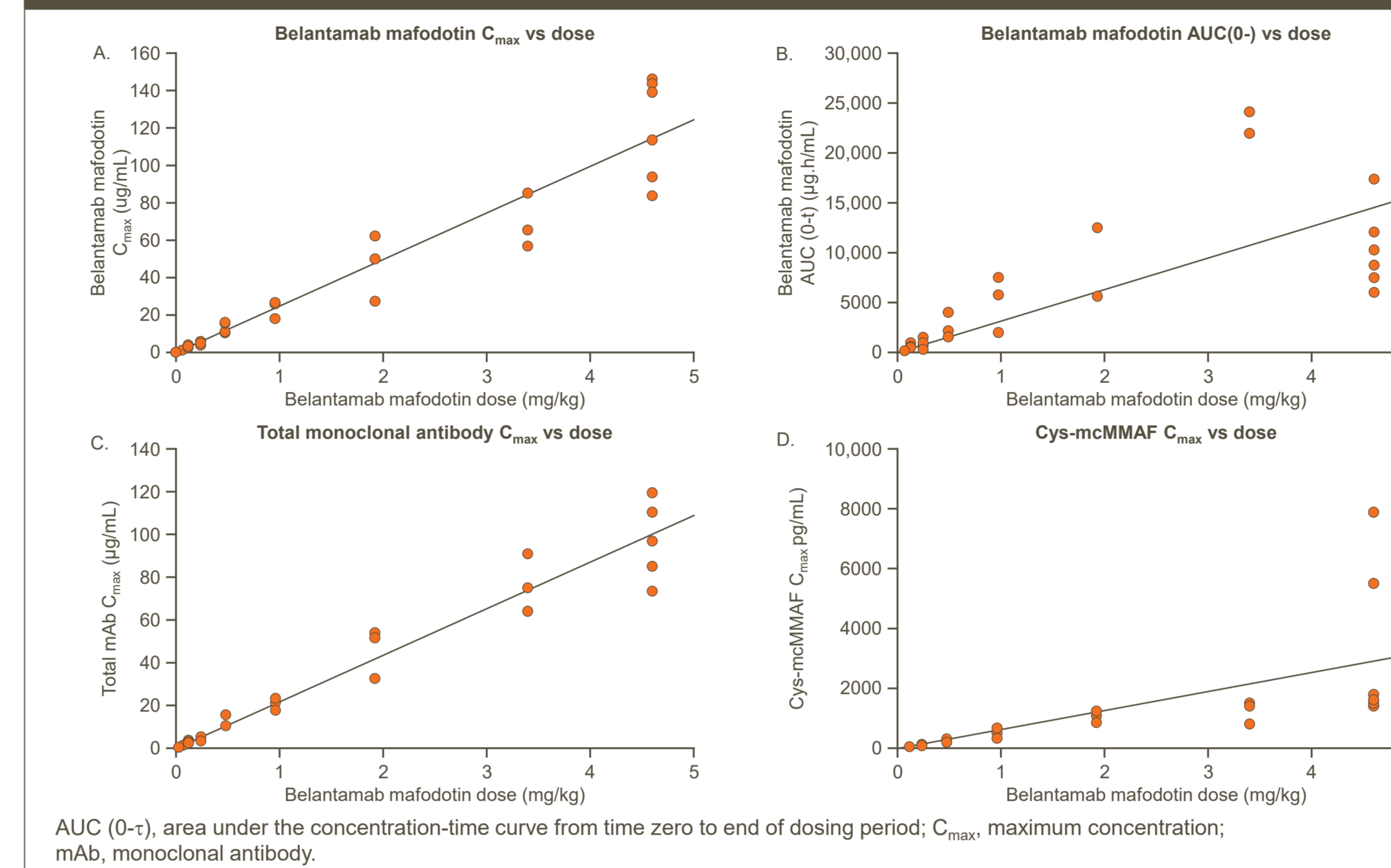
- Plasma exposures of belantamab mafodotin, total BCMA mAb and cys-mcMMAF appeared to increase proportionally with dose (Figure 3).

### 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 <sub>(0-∞)</sub> (µg·h/mL)	NC	200.5	633.4 (35)	729.4 (91)	2389 <sup>a</sup> (51)	4448 (80)	9893 <sup>a</sup> (52)	NC	23122 <sup>b</sup> (7)	9739 (39)	NC
C <sub>max</sub> (µg/mL)	0.43	1.32	2.96 (18)	4.55 (20)	11.9 <sup>a</sup> (24)	23.1 (23)	43.8 <sup>a</sup> (45)	NC	68.1 (21)	117 (24)	NC
T <sub>max</sub> (h)	2.08	4.08	1.19 (1.00–2.00)	3.09 (2.00–8.78)	1.00 <sup>a</sup> (1.00–4.00)	2.05 (2.00–2.08)	1.00 <sup>a</sup> (0.50–24.00)	NC	6.92 (2.02–8.78)	1.56 (0.95–2.07)	2.00 <sup>a</sup> (0.50–24.00)
C <sub>trough</sub> (ng/mL)	NC	NC	382 (106)	1331 <sup>a</sup> (44)	4307 <sup>a</sup> (114)	3720 (114)	11421 <sup>a</sup> (36)	3727 (50)	28134 <sup>a</sup> (36)	2301 (76)	NC
CL (mL/h)	NC	28.3	10.5 (59)	25.0 <sup>a</sup> (89)	15.1 <sup>a</sup> (75)	8.46 <sup>a</sup> (27)	11.7 <sup>a</sup> (27)	NC	NC	38.8 <sup>a</sup> (38)	17.9 <sup>a</sup> (83)
V <sub>ss</sub> (L)	NC	5239	2.90 (29)	4.29 <sup>a</sup> (31)	4.39 <sup>a</sup> (22)	3.22 <sup>a</sup> (22)	5.16 <sup>a</sup> (27)	NC	NC	5.225 <sup>a</sup> (19)	4.08 <sup>a</sup> (32)
t <sub>1/2</sub> (days)	NC	5.26	7.84 (37)	4.91 <sup>a</sup> (76)	8.27 <sup>a</sup> (50)	11.0 <sup>a</sup> (47)	12.9 <sup>a</sup> (27)	NC	NC	4.32 <sup>a</sup> (17)	6.69 <sup>a</sup> (54)

Data presented as geometric mean (%CV), except  $T_{max}$  which is presented as median (minimum–maximum). <sup>a</sup>n=1; <sup>b</sup>n=2; <sup>c</sup>n=3; <sup>d</sup>n=4; <sup>e</sup>n=18; <sup>f</sup>n=28. AUC<sub>(0-∞)</sub>, area under the concentration-time curve from time zero to end of dosing period; C<sub>max</sub>, maximum concentration; CL, clearance; C<sub>trough</sub>, trough concentration; NC, not calculated; t<sub>1/2</sub>, half-life; T<sub>max</sub>, time to C<sub>max</sub>; V<sub>ss</sub>, variation of biomass concentration

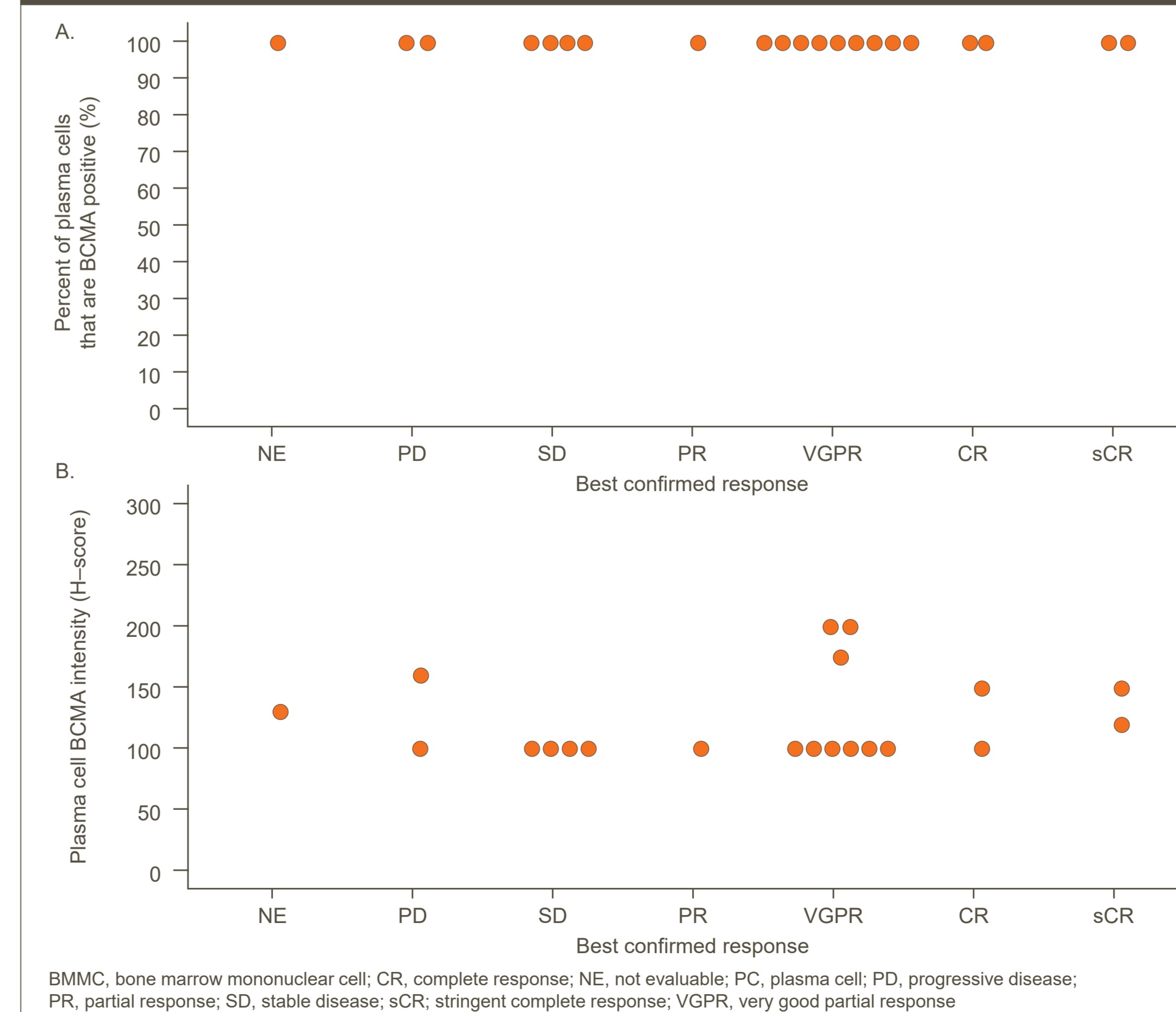
### Figure 3. Plasma exposures of A) belantamab mafodotin (C<sub>max</sub>), B) belantamab mafodotin (AUC), C) total anti-BCMA mAb (C<sub>max</sub>) and D) cys-mcMMAF (C<sub>max</sub>) by dose level (Part 1)



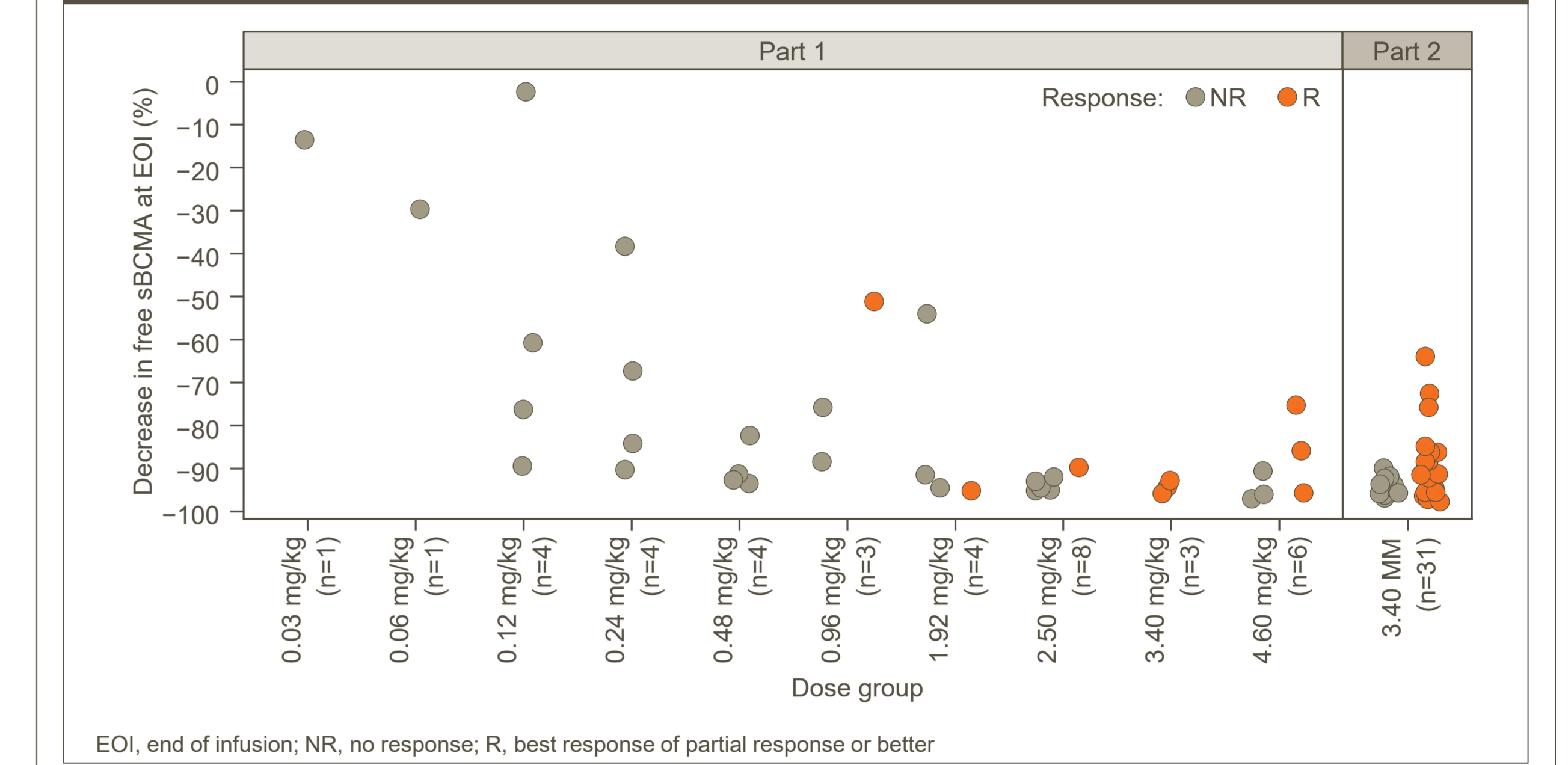
### Biomarkers

- 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).

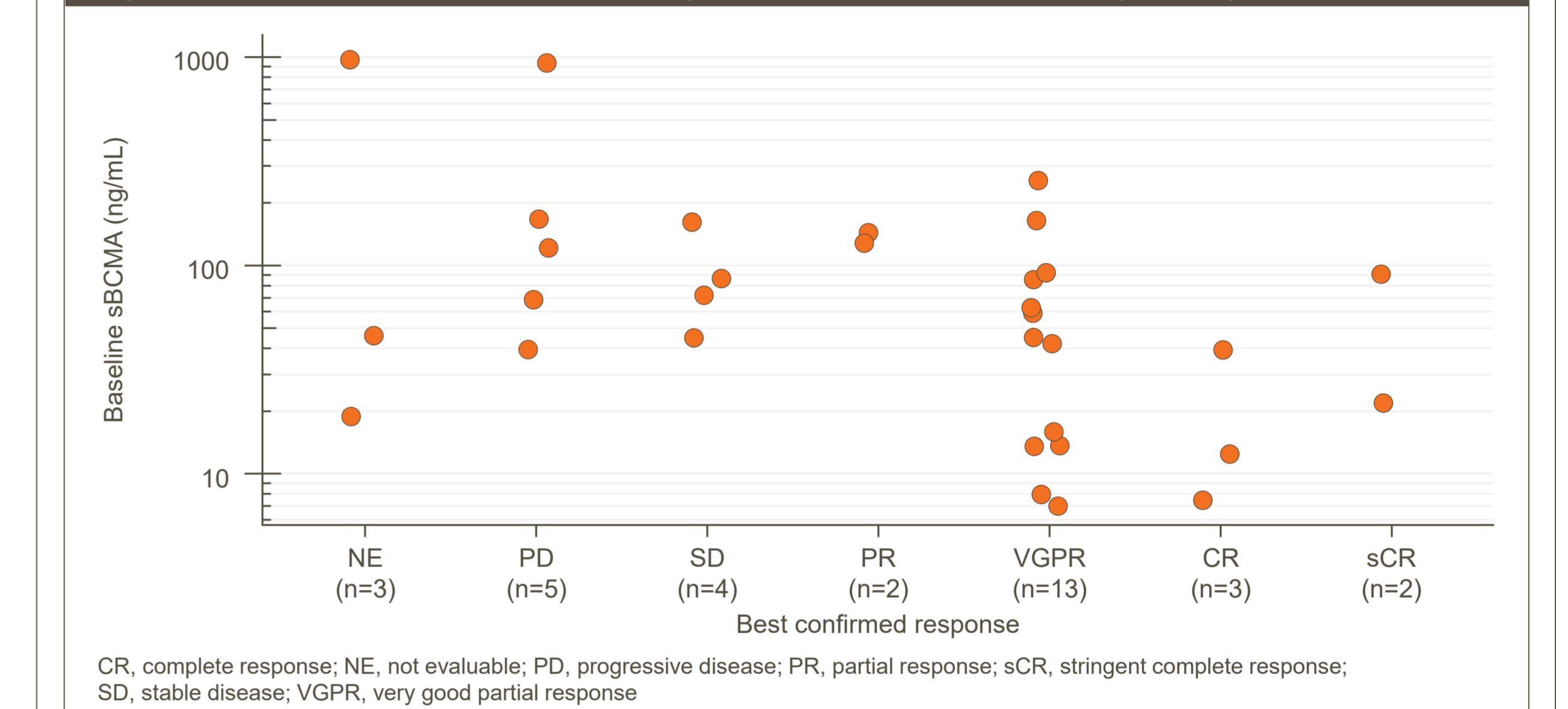
### Figure 4. Baseline BCMA expression in A) Myeloma BCMA expression and B) myeloma BCMA intensity



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



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



## 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<sup>6</sup> compared with interim analysis.<sup>5</sup>
- 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.<sup>7</sup>
- 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.

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## Disclosures

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