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Title: **Targeting B-Cell Maturation Antigen with GSK2857916 Antibody-Drug Conjugate in Relapsed or Refractory Multiple Myeloma: A Dose-Escalation and Expansion Phase 1 Trial (BMA117159)**

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ABSTRACT

Background: B-cell maturation antigen (BCMA) is a tumour necrosis superfamily cell-surface receptor required for plasma cell survival. This study evaluated safety, tolerability and clinical activity of GSK2857916, a novel anti-BCMA antibody conjugated to microtubule-disrupting agent monomethyl auristatin-F, in patients with relapsed/refractory multiple myeloma (MM).

Methods: This international, multicentre, open-label, first-in-human Phase 1 study comprised dose escalation (Part 1) and dose expansion (Part 2) phases. Adults with histologically or cytologically confirmed MM, ECOG performance status 0/1, and progressive disease following stem cell transplant, alkylators, proteasome inhibitors and immunomodulators were recruited. In Part 1, patients received GSK2857916 (0·03–4·6 mg/kg) via 1-hour intravenous infusion. In Part 2, patients received the selected dose of GSK2857916 (3·4 mg/kg) every 3 weeks. Primary endpoints were maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D). Additional endpoints included pharmacokinetics and preliminary anti-cancer activity assessments. All patients who received ≥1 dose were included in analyses. The study is ongoing and registered with ClinicalTrials.gov (NCT02064387).

Findings: Between July 2014 and February 2017, 73 patients were treated (Part 1 n=38; Part 2 n=35). No MTD was identified in Part 1. Based on safety/efficacy, 3·4 mg/kg was selected as RP2D. Corneal events were common (42/73; 58%); most (37/42) were Grade 1/2 and did not result in treatment discontinuation in Part 2. The other most common Grade 3/4 events were thrombocytopenia (25/73; 34%) and anaemia (11/73; 15%). There were 12 treatment-related serious AEs and no treatment-related deaths. The ORR at 3·4 mg/kg in Part 2 was 60% (21/35; 95% confidence interval [CI]: 42·1%–76·1%), with a median progression-free survival of 7·9 months (95% CI: 3·1 – not estimable).

Interpretation: At the identified RP2D, GSK2857916 is well tolerated and demonstrates good clinical efficacy in heavily pretreated patients, suggesting it is a promising candidate for the treatment of relapsed/refractory MM.

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RESEARCH IN CONTEXT

Evidence before this study: New approaches to the treatment of relapsed refractory myeloma are urgently needed. GSK2857916 provides such an advancement by targeting B-cell maturation antigen (BCMA), which is universally expressed in patients with multiple myeloma. We searched PubMed with the terms “relapsed”, “myeloma”, “BCMA”, and “clinical trial” for studies published from 1 January 1990 to 1 January 2018. We identified multiple trials evaluating BCMA-targeted chimeric antigen receptor T cell and related adoptive cellular approaches but no published studies in humans of BCMA-targeted antibodies or antibody-drug conjugates.

Added value of this study: This is the first Phase 1 trial of the novel anti-BCMA antibody-drug conjugate GSK2857916 in humans. The data demonstrate that GSK2857916 has significant activity in patients with heavily pretreated, relapsed/refractory myeloma, with 60% ORR and primary toxicities of corneal events and thrombocytopenia. The depth and durability of responses seen with GSK2857916 in this population are promising and compare favourably with those observed previously for any approved single agent. The results further validate BCMA as an attractive target for multiple myeloma. GSK2857916 could potentially offer a new treatment option for patients with multiple myeloma that is steroid free and off the shelf with a convenient administration schedule.

Implications of all the available evidence: These results provide strong evidence that targeting BCMA with an antibody-drug conjugate is effective in the treatment of advanced relapsed/refractory multiple myeloma. GSK2857916 had a manageable safety profile, and significant clinical efficacy in patients with multiple myeloma with limited treatment options. Additional monotherapy and combination studies are in development.

INTRODUCTION

Recent progress in immunotherapy has significantly improved the prognosis for patients with multiple myeloma (MM).[1] However, outcomes remain poor for those with relapsed and refractory disease. Patients who are refractory to both proteasome inhibitors (PI) and immunomodulatory drugs (IMiD) have an estimated survival of only 13 months.[1] As such, the development of novel therapeutics to treat this disease is critical.

The normal function of B-cell maturation antigen (BCMA) is to promote the survival of B cells at later stages of differentiation, including plasma cells.[2] Mice lacking expression of BCMA demonstrate a reduced number of long-lived bone marrow plasma cells but have an otherwise normal phenotype.[3] BCMA membrane expression is present on a subset of normal late-stage B cells and is universally detected on normal and malignant plasma cells, including MM cells.[2,4,5] Blocking of BCMA signalling has been shown to inhibit cell growth and survival in MM cells in preclinical studies.[6] Soluble BCMA has been implicated in the reduction of polyclonal antibody levels and MM-associated immune deficiency.[5] Higher BCMA levels are detected in patients with MM with progressive disease when compared with those with responsive disease, and correlate with reduced survival.[7] Although the precise physiological implications of BCMA on myeloma cell growth and survival are unknown, the restricted expression profile of BCMA and its survival function in plasma cells make it an attractive target in this disease.

GSK2857916 is a humanised immunoglobulin (Ig)G1 monoclonal antibody-drug conjugate that binds specifically to BCMA.[8] The parent antibody (GSK28579164) is conjugated to the tubulin polymerisation inhibitor monomethyl auristatin-F (MMAF) via a protease-resistant maleimidocaproyl linker. Upon binding to the cell surface, GSK2857916 is rapidly internalised

and active cytotoxic drug (cys-mcMMAF) is released inside the cell.[4] Additionally, the antibody is afucosylated, which increases binding to FcγRIIIa receptors, enhances recruitment and activation of immune effector cells, and enhances the killing of tumour cells by antibody-dependent cellular cytotoxicity.[8] The potential immunogenic cell death mechanism has been shown to further induce macrophage-mediated phagocytosis.[8] These various mechanisms of action result in significant in vitro and in vivo activity against myeloma cell lines and primary patient myeloma samples.[4] Based on these encouraging non-clinical data, we undertook a Phase 1 first-in-human, open-label study to assess the safety and tolerability of GSK2857916 monotherapy in patients with relapsed/refractory MM.

METHODS

Study Design and Participants

This study was performed at 9 centres in the USA, Canada and United Kingdom (for further details see Supplementary Appendix, p5). The study comprised two parts. The Part 1 dose-escalation phase assessed the safety and tolerability of GSK2857916 to identify the recommended Phase 2 dose (RP2D). Neuenschwander continual reassessment method (N-CRM)[9] was utilized to inform the dose escalation decisions. Part 2 evaluates the safety, tolerability, pharmacokinetics, and clinical activity of the dose level identified in Part 1. Data for patients with MM are reported here; data for patients with BCMA-positive B-cell lymphoma (currently enrolling in Part 2) will be reported separately.

For Part 1, eligible adult (≥18 years of age) patients had a confirmed diagnosis of MM; prior therapy with alkylators, PI, and IMiD; and were refractory to the last line of treatment, defined as progression on or within 60 days of completion of the last therapy.

For Part 2, patients met the eligibility criteria for Part 1, in addition to having measurable disease as defined by the International Myeloma Working Group (IMWG) criteria.[10]

All patients had adequate hepatic (total bilirubin ≤1·5 times and aspartate transaminase and alanine transaminase ≤1·5 times the upper limit of the normal range), haematological (absolute neutrophil count ≥1·0 x 10^9/L, haemoglobin ≥8·0 g/dL, and platelets ≥50 x 10^9/L), and renal function (creatinine clearance ≥50 mL per minute for patients enrolled in Part 2) at screening.

There was no prospective selection of patients based on tumour, or soluble BCMA expression. Full inclusion and exclusion criteria are provided in the Supplementary Appendix, p3.

BMA117159 (ClinicalTrials.gov identifier: NCT02064387) was designed by the lead authors and sponsor; the study protocol summary is provided in the Supplementary Appendix, p19–285. It was conducted according to principles of Good Clinical Practice after approval by regulatory authorities and institutional review boards at each study site. All patients provided written informed consent.

Procedures

GSK2857916 (GSK Manufacturing SpA, Parma, Italy; Baxter Oncology GmbH, Halle/Westphalia, Germany) at doses ranging between 0·03 mg/kg and 4·60 mg/kg was administered as a 1-hour intravenous infusion every 3 weeks for a maximum of 16 cycles. This schedule was chosen based on preclinical testing, patient convenience, and expected pharmacokinetic properties of an IgG1-based antibody-drug conjugate.[11,12] The option to explore an additional dose-escalation cohort with a once-weekly dosing schedule was included in the

protocol, but after evaluation of clinical and pharmacokinetic data from the every-3-week dosing cohort, it was not pursued. Prophylaxis for infusion-related reactions (IRRs) was not permitted for the first infusion to enable the assessment of the frequency and severity of IRRs with first dose, but could be administered for subsequent infusions at the discretion of the investigator. All patients received steroid eye drops with each infusion to mitigate corneal events, a known toxicity of MMAF (prednisolone phosphate 1% or dexamethasone 0·1% 4 times a day for 4 days, starting 1 day prior to each dose).[13] Patients remained on treatment until progression, unacceptable toxicity, consent withdrawal, or completion of 16 doses of treatment. Dose modifications were allowed according to pre-defined criteria based on the nature of the event and toxicity grade.

Data on adverse events (AEs) were collected from the time of first dose administration until 30 days following discontinuation of study treatment. Ophthalmology examinations were conducted prior to the start of each cycle. Laboratory monitoring (haematology, clinical chemistry, urinalysis) was performed on screening, weekly during Cycle 1, then at the start of each subsequent cycle and end of study treatment. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4·0.[14]

Clinical activity of GSK2857916 was assessed in accordance with the IMWG Uniform Response Criteria for Multiple Myeloma.[15] Disease assessment for evaluation of response was completed within 4 weeks prior to the first dose, and at the start of each cycle until the final study visit. In patients with extramedullary disease, assessment included imaging (e.g. computed tomography scan, magnetic resonance imaging, bone scan, plain radiography) prior to Cycles 5, 9 and 13, and physical examination (as indicated for palpable/superficial lesions) at the start of each cycle.

The pharmacokinetics of GSK2857916 (intact antibody-drug conjugate), unbound antibody, total antibody, and free cys-MMAF were assessed from blood samples taken pre-dose and at 1 hour (end of infusion) during Cycles 1–5. Additional samples were collected during Cycle 1 on Days 1, 8, 15 and 22 (Cycle 2 pre-dose).

Soluble BCMA (free and complex) was assessed using mesoscale discovery (MSD) immunoassays pre-dose, at end of infusion, and 24 hours post-end of infusion on Day 1, and on Days 8, 15 and 22; additional samples were collected every 21 days. MSD immuno-assays were validated and performed by GlaxoSmithKline (King of Prussia, PA) (Supplementary Appendix, p3). During validation, the range of free soluble BCMA in healthy donors (n=25) was determined to be 3·23–10·68 ng/mL with a median value of 6·69 ng/mL (see Supplementary Appendix, p4).

Outcomes

The primary endpoints of the trial were to determine the safety, tolerability, maximum tolerated dose (MTD) and RP2D and schedule of GSK2857916. The MTD was defined as the dose which has the highest probability of having a dose limiting toxicity (DLT) rate within the target toxicity interval and for which the probability that the DLT rate lies within the excessive toxicity or the unacceptable toxicity window is less than 25%. DLT criteria are listed in the Supplementary Appendix, p3. RP2D was defined as MTD, or a dose lower then MTD that provides 95%–100% receptor occupancy, with no evidence of target mediated disposition in the pharmacokinetic profile and demonstrating signs of clinical activity. Secondary endpoints were pharmacokinetic profile (single dose AUC, C_{max}, t_{max}, clearance, V_{ss}, $t_{½}$; repeat dose C_{max} and C_{trough}), the incidence of anti-drug antibodies, and clinical activity measured as overall response

rate (ORR), defined as the percentage of subjects achieving confirmed partial response or better (≥PR) and clinical benefit rate, defined as the percentages of subjects with minimal response or better (≥MR). The dose for Part 2 expansion was chosen based on review of the totality of the safety, tolerability, efficacy and pharmacokinetic data during Part 1.

Statistical Analysis

The data presented here are an interim analysis of data as of the data cut-off date of Monday 26 June 2017. Software used included SAS version 9.4, SAS version 9.2 (SAS Institute, Cary, CA, USA) for pharmacokinetic analyses, and Fixed and Adaptive Clinical Trial Simulator (FACTS) version 2.3 or higher for N-CRM model implementation.

The sample size for each dose level in Part 1 was determined by pre-defined criteria with a single subject cohort run-in (cohort size =1 for each dose level) until occurrence of a ≥Grade 2 toxicity, for which a relationship to GSK2857916 cannot be ruled out, and which occurs in one subject in Cycle 1 (21 days). At this point, the cohort size would be expanded to 3 or more subjects and the escalation will continue to follow the N-CRM procedure. Overall, it was anticipated that approximately 30 patients would be required to establish the MTD or RP2D in Part 1 of the study with testing up to the ~4·6 mg/kg dose where clinical activity was expected based on preclinical testing. An additional intermediate dose level of 2·5 mg/kg was evaluated in Part 1 to investigate the emergent trend towards an increased frequency of higher grade corneal events in treated patients.

Demographics and safety data were descriptively summarised. ORR was reported with two-sided 95% exact confidence intervals (CI). Time-to-event endpoints, including progression-free survival, duration of response, and time to response were analysed descriptively with the

Kaplan–Meier method for Part 2 only, retrospectively. Subgroup analyses were performed retrospectively; the results should be interpreted with caution due to small sample sizes. All patients who received at least one dose of GSK2857916 were included in analyses. Pharmacokinetic parameters were estimated using model-based population pharmacokinetic methods.

This study is registered with ClinicalTrials.gov, NCT02064387.

Role of the funding source

Study BMA117159 was funded by GlaxoSmithKline. The sponsor was involved in study design, collection and interpretation of data, and the writing of the report. All authors had full access to the data upon request, and were involved in data interpretation, manuscript preparation, revision, and final approval. The authors vouch for the accuracy of the data and adherence to the study protocol. The corresponding author had the final responsibility to submit for publication.

RESULTS

This is an ongoing study; enrolment of patients with MM took place from 29 July 2014 to 21 February 2017. Data for some pharmacokinetic assessments and the incidence of anti-GSK2857916 will be reported separately. As of the data cut-off date of 26 June 2017, 38 patients received at least one dose in Part 1 and 35 received at least one dose in Part 2 (Figure 1).

The baseline characteristics and patient disposition for Part 1 are shown in Supplementary Appendix, p6 and for Part 2 are summarised in Table 1 and Supplementary Appendix, p7. For patients in Part 2: the median time from diagnosis was 3·8 years (range: 1–10); the majority of patients were heavily pretreated, with 20 (57%) having received ≥5 prior lines of therapy (range: 1– >10); 31(89%) were double-refractory to a PI and IMiD and 13 (37%)

were refractory to daratumumab; 12 (34%) had prior daratumumab and were also double refractory to PI and IMiD; and 31 (89%) had previously undergone stem cell transplant.

For those patients in Part 2 in whom GSK2857916 was initiated at 3·4 mg/kg, at the time of data cut-off, the overall median duration of follow-up was 6·6 months (range: 1–10) with a median administration of 5 infusions (range: 1–13); 22 (63%) patients were still on study (Table 1). Of those who discontinued treatment (n=18), 15 (43%) discontinued due to disease progression and 2 (6%) due to AEs.

In Part 1, doses ranging from 0·03 mg/kg to ~4·6 mg/kg, administered every 3 weeks, were explored. Detailed results of Part 1 are reported in the Supplementary Appendix, p8–11, p14, 15, 17). Overall, no dose-limiting toxic events were observed and thus no MTD was established (Supplementary Appendix, p8). The most common treatment-emergent AEs, serious AEs, and corneal events for Part 1 are listed in Supplementary Appendix, p9–11. There was one death in Part 1, which was attributed to disease progression and not deemed treatment-related. Although patient numbers for individual dose groups were small, there was a trend towards increased frequency of Grade 3/4 corneal events with increasing dose (Supplementary Appendix, p8). Therefore, an additional dose level of 2·5 mg/kg, not included in the initial dose-escalation period, was later assessed to further characterise this apparent trend. Corneal events were still observed at 2·5 mg/kg, but no patients treated in this cohort had a response (n=8) as of the data cut-off date of 26 June 2017.

The clinical responses (including stratification by dose) and duration of study treatment are summarised in Supplementary Appendix p8 and p14. At doses between 0·03 and 2·5 mg/kg (n=29), there were two responses (one PR at 0·96 mg/kg and one very good partial response

[VGPR] at 1·92 mg/kg), whereas 6/9 patients treated at 3·4 and 4·6 mg/kg responded (two PR, three VGPR, and one stringent complete response [sCR]), with four ongoing responses (duration of response range: 7·98–13·08 months; duration of study treatment range: 340+ to 400+ days) at time of data cut-off.

Based on estimated receptor saturation at doses ≥1·92 mg/kg (see Pharmacokinetics section), a 100% response rate observed in the 3 patients receiving 3·4 mg/kg, a lack of observed clinical activity in the 8 patients treated at 2·5 mg/kg, and low tolerability of the ~4·6 mg/kg dose (fevers, severe fatigue, and headache), the recommended dose for Part 2 was set at 3·4 mg/kg.

The most common treatment-emergent AEs for Part 2 are listed in Table 2. All patients in Part 2 experienced at least one AE. The most common events occurring in ≥25% of patients were corneal events, thrombocytopenia (including the preferred term platelet count decreased), anaemia, aspartate aminotransferase increased, and cough. Corneal events included but were not limited to blurry vision, dry eyes, photophobia, and others (see Supplementary Appendix, p12). Grade 3/4 AEs were reported in 28 (80%) of 35 patients in Part 2 (54/73 (74%) in Parts 1 and 2 overall; Table 2 and Supplementary Appendix, p9). In Part 2, serious AEs were reported in 14 (40%) patients, most commonly IRRs and lung infection (2 patients each). Five (14%) patients had serious AEs that were considered related to the study drug by the investigator, including IRR (n=2), intracranial haemorrhage (n=1), lung infection and pyrexia (n=1), and pericardial effusion (n=1). The single patient with intracranial haemorrhage had a history of intracranial bleeding and pre-existing thrombocytopenia that worsened post treatment in the setting of disease progression.

In Part 2, 23 (66%) patients had AEs that led to dose reduction, and 25 (71%) patients had AEs that led to dose interruptions or delays (Supplementary Appendix, p8 and 13). Two patients discontinued treatment due to AEs: thrombocytopenia (2 patients [6%]) and increased

blood creatinine phosphokinase (1 patient [3%], who was one of the 2 patients who experienced thrombocytopenia). As of 26 June 2017, there were three deaths in Part 2, all of which were attributed to progressive myeloma and not deemed treatment-related.

AEs of clinical interest related to GSK2857916 included IRRs, thrombocytopenia, and corneal events. In order to fully evaluate the incidence and severity of IRRs, pre-medications were prohibited prior to the first infusion. In Part 2, 8 (23%) patients experienced IRRs; most (5/8) were Grade 1/2 and all occurred with the first dose. Following the first infusion, pre-medications were permitted and included paracetamol (n=8, 23%), antihistamines (n=7, 20%), steroids (n=2, 6%; dexamethasone, hydrocortisone sodium succinate), and sodium chloride (n=1, 3%). Any-grade and Grade 3/4 thrombocytopenia occurred in 20/35 (57%) and 12/35 (34%) of patients, respectively. The median time to first occurrence of thrombocytopenia was 7 days (range: 1–185) and the median duration for patients with a resolution date (n=9) was 8 days (range: 6–16). Two (6%) patients discontinued treatment and 7 (20%) required dose reduction or delays due to thrombocytopenia.

Corneal events were reported in 22/35 (63%) patients in Part 2 and 42/73 (58%) in Parts 1 and 2 overall (Supplementary Appendix, p12). These were predominantly mild to moderate (Grade 1/2) (19/22 in Part 2; 37/42 in Parts 1 and 2 overall; Supplementary Appendix, p12); 3 (9%) patients in Part 2 experienced Grade 3 corneal events (1 with keratitis, 1 with eye pain and keratitis, and 1 with dry eye). The median time to onset of corneal events was 23 days (range: 1–84) and the median duration for patients with a resolution date (n=13) was 30 days (range: 5–224). Eighty-nine percent of patients had corneal findings on ophthalmic examination characterised by a superficial punctate keratitis (n=27/35; 77%) often associated with epithelial (microcystic) oedema (n=22; 63%) and stromal oedema (n=5; 14%), or opacities (n=8; 23%). As

of 26 June 2017, data on corneal examination were available for 13 patients with an end of treatment visit. Eleven of these 13 patients had corneal abnormalities on ophthalmic examination; most (9/11) were considered mild. While visual acuity assessed by Snellen method declined in most patients during treatment, by the end of treatment, possible or definite worsened vision (change from baseline in best corrected visual acuity score ≥0·3) was evident in 3/13 and 5/12 patients with available data, in the right and left eye, respectively. Management of corneal events included dose reduction in 14 (40%) patients and/or dose interruptions or delays in 15 (43%) patients, and supportive measures, such as the use of artificial tears and increasing the duration or frequency of steroid eye drop treatment. No patient in Part 2 permanently discontinued study treatment due to a corneal event. This study is ongoing, hence full information on resolution of corneal events was not available at data cut-off.

The confirmed ORR in Part 2 was 60% (95% CI: 42·1–76·1) with 1 (3%) patient achieving a sCR, 2 (6%) achieving a CR, 15 (43%) achieving a VGPR, and 3 (9%) achieving a PR (Figure 2A and Figure 3A). Retrospective exploratory subgroup analyses revealed the ORR for those with high-risk cytogenetics (n=8) was 63% (95% CI: 24·5–91·5) (Figure 2B) and 42% (95% CI: 15·2– 72·3) for those who received prior daratumumab and were double refractory to PI and IMiD (n=12). In addition, the ORR was 68·2% (95% CI: 45·1–86·1) in patients treated with ≤5 prior lines of treatment, and was 46·2% (95% CI: 19·2–74·9) in patients who had received >5 lines of therapy, (Figure 2B) (post hoc analysis).

The median time to first response in Part 2 was 1·4 months (95% CI: 0·8–2·0). Despite dose interruptions and reductions for toxicities, responses were maintained and in some cases deepened (Figure 3B). With a median follow-up of 6·6 months (range 1–10 months), the median progression-free survival (post hoc analysis) was 7·9 months (95% CI: 3·1–not estimable)

(Figure 4A), and the median duration of response was not estimable (Figure 4B); however, the 25th percentile for duration of response was 6·7 months (95% CI: 1.6–not estimable). Survival data were immature at the data cut-off date.

At the end of the infusion, free soluble BCMA levels decreased by approximately 10-fold relative to baseline levels and were restored to baseline after 7 days (Supplementary Appendix, p15). Pre-dose (Cycle 1) free soluble BCMA levels were compared with response (as measured by reduction from baseline in serum and urine M-protein and serum free light chain concentrations), but no clear relationship was evident (Supplementary Appendix, p16).

Maximum concentrations of GSK2857916, parent antibody, and total antibody were observed at end of infusion, whereas cys-mcMMAF concentrations peaked approximately 24 hours after dosing (Supplementary Appendix, p17). There was limited accumulation of GSK2857916 and cys-mcMMAF during subsequent cycles, and cys-mcMMAF molar ratio was <1% compared with GSK2857916. The pharmacokinetics of GSK2857916 were linear, dose proportional and well described using population pharmacokinetic methods with conventional allometry. GSK2857916 was cleared slowly with total plasma clearance of 0·37 L/d, and steady-state volume of distribution was typical for a monoclonal antibody (4·2 L), implying confinement mainly in systemic circulation and interstitial space. The terminal phase half-life of GSK2857916 was 8–9 days (consistent with limited accumulation).

The levels of free soluble BCMA fell from pre-dose levels in a dose-dependent manner 24 hours after infusion, with maximum reductions achieved at doses ≥1·92 mg/kg (Supplementary Appendix, p15). Soluble BCMA complex levels increased accordingly, with saturation reached at similar doses.

DISCUSSION

This ongoing, first-in-human study demonstrates that the novel anti-BCMA antibody-drug conjugate GSK2857916 has significant single-agent activity in patients with relapsed/refractory MM, with 21 (60%) of 35 patients achieving PR or better at the RP2D of 3·40 mg/kg. Patients were heavily pretreated, including 31/35 (89%) patients who were double-refractory to a PI and IMiD, and 13/35 (37%) patients who were refractory to daratumumab. In this context, the response depth, including 18/35 (51%) patients with VGPR or better, and median progression-free survival of 7·9 months are notable (95% CI: 3.1 months–not estimable). Even among patients with prior daratumumab treatment and refractory to both PI and IMiD, the ORR was 42%.

The RP2D of 3·4 mg/kg was selected based on the acceptable balance between clinical response and tolerability. The highest dose tested (4·6 mg/kg) was considered to be not tolerated. Although only 3 patients received the 3·4 mg/kg dose in Part 1, they all achieved a response (1 each of VGPR, sCR, and PR). The dose selection is further supported by BCMA receptor saturation observed at doses ≥1·92 mg/kg; although in a wider patient population, receptor saturation may potentially be affected by variability in soluble BCMA levels.

The depth and durability of responses seen with GSK2857916 in this population are promising and compare favourably with those described previously for any approved single agent, although the small sample size necessitates caution in data interpretation. Neither the anti-SLAMF7 antibody elotuzumab nor the histone deacetylase inhibitor panobinostat had significant single-agent activity.[16,17] In Phase 2 studies of carfilzomib monotherapy[18] and pomalidomide alone or pomalidomide plus dexamethasone,[19] responses were observed in only a minority of patients (24%, 18%, and 33%, respectively) with median progression-free survival rates of 3·7,

2·7, and 4·2 months, respectively. In the pivotal Phase 2 monotherapy study of the anti-CD38 antibody daratumumab, in which 64% of patients were refractory to lenalidomide and bortezomib, the ORR and median progression-free survival at the approved 16 mg/kg dose were 36% and 5·6 months, respectively. Only 10% of patients achieved VGPR or better with daratumumab.[20]

The present results also demonstrate a manageable safety profile relative to currently available agents.[21] Thrombocytopenia and corneal events were the most frequently reported AEs and are consistent with the known toxic effects of MMAF and other MMAF-linked antibody-drug conjugates.[13] These are in contrast to the neurological and pulmonary toxicities attributed to brentuximab vedotin, which employs MMAE.[22] The corneal events most often manifested as blurry vision, photophobia, and dry eyes though a range of symptoms was possible, including increased lacrimation, pain and pruritus. Most events were Grade 1/2 and improved with dose interruptions and/or reduction. Dry eye and keratitis were the most common Grade 3 events; no Grade 4/5 events were reported and no patients discontinued because of corneal events in Part 2. Most patients did have corneal findings on examination, most commonly superficial punctate keratitis. For the 13 patients with end of treatment corneal examinations available as of 26 June 2017, the majority had findings classified as mild in severity. Furthermore, decline in visual acuity was found to have improved in the majority of those with available data at the end of the treatment visits. Importantly, while the lower starting doses of GSK2857916 tested in dose escalation were associated with lower response rates, reducing the dose to 2·5 or 1·7 mg/kg after achieving a response in Part 2 or delaying dosing to allow for recovery from toxicities did not appear to induce loss of response. Nevertheless, given the high rate of dose modifications, additional investigations into strategies to mitigate corneal events are warranted.

Thrombocytopenia in most cases recovered between doses, and few bleeding events were reported. Infusions were administered over 1 hour and were associated with mostly Grade 1/2 IRRs.

An inherent limitation of Phase 1 study design is the necessarily small sample size; future later phase studies will provide more robust data on the clinical efficacy and safety profile of GSK2857916. As this is an ongoing study, additional data on potential long-term sequelae and also resolution of corneal events should be available on analysis of the final data. In addition, analyses of patients previously treated with daratumumab combinations will be performed in the future.

The target of GSK2857916 differentiates it from other monoclonal antibodies currently in the clinic for myeloma. BCMA is expressed universally on normal and malignant plasma cells, but not on non-haematopoietic cells or haematopoietic stem cells.[23-25] Unlike SLAMF7 or CD38, the targets for elotuzumab and daratumumab, respectively, it is not expressed on natural killer cells, T cells, monocytes, red blood cells, or lymphoid progenitor cells.[8,24] In vitro testing of GSK2857916 against myeloma cells show that BCMA is recycled to the cell surface after binding and internalisation.[4] Although previous studies have shown that gamma-secretase causes ongoing shedding of non-bound BCMA from plasma cells,[26] whether overall BCMA expression on residual myeloma cells will be down-regulated after treatment, as has been described in occasional patients following BCMA chimeric antigen receptor (CAR) T cells,[27,28] as well as with CD38 following daratumumab treatment,[25] remains to be determined.

Published data indicate that high levels of soluble BCMA exist in patients with MM, particularly in those with advanced disease, which could potentially interfere with the binding of GSK2857916 to BCMA or act as a drug sink.[5,7,26] This could theoretically affect both safety and

efficacy, especially in patients with high soluble BCMA levels. Based on currently available data, there was no obvious relationship between reduction from baseline in M-protein (or free light chain) measurement and pre-dose (Cycle 1) soluble BCMA levels (Supplementary Appendix, p16).

The clinical activity of GSK2857916 expands on the initial promising reports targeting BCMA using CAR T cells,[27,28] as well the preclinical activity of T cell-dependent bispecific antibodies against BCMA now entering the clinic,[29] further validating BCMA as an attractive target for myeloma immunotherapy. However, unlike these approaches, GSK2857916 does not require a labour-intensive manufacturing process or treatment at a specialised centre, and is not associated with potentially severe toxicities such as cytokine release syndrome and encephalopathy.[28,30]

The activity of GSK2857916 may be a result of its ability to target myeloma cells via several different mechanisms of action. In addition to exerting direct anti-tumour activity against proliferating cells by delivering a potent anti-mitotic drug, it induces antibody-dependent cellular cytotoxicity via enhanced binding to multiple FcR-expressing immune effector cells, allowing it to target non-dividing myeloma cells. This utilisation of immune effector cells provides a rationale for combination with IMiDs; indeed, lenalidomide augmented the activity of GSK2857916 efficacy against MM cells in vitro.[23] This mechanism also differentiates it from other antibody-drug conjugates under development for myeloma that have failed to demonstrate significant single-agent activity in myeloma, including lorvotuzumab mertansine (an anti-CD56-maytansinoid)[31] and indatuximab ravtansine (an anti-CD138-maytansinoid).[32] Finally, data further suggest the potential of GSK2857916 to induce immunogenic cell death of myeloma cells,[8] which may stimulate endogenous anti-myeloma immunity and thereby contribute to

durability of responses observed in this heavily pretreated population.

In conclusion, this first trial of GSK2857916 provides evidence that targeting BCMA is effective in the treatment of advanced MM. GSK2857916 showed a favourable administration schedule and safety profile and significant clinical efficacy in patients with MM with limited treatment options. Its target and mechanisms of action are distinctive, and additional monotherapy and combination studies are in development.

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DECLARATIONS OF INTEREST

LDA has participated in speakers' bureaux for Celgene, Takeda and Amgen. ADC is a consultant for and a member of an advisory board for GlaxoSmithKline and Celgene, is a member of an advisory board for Janssen and Bristol-Myers Squibb, has received research funding from Bristol-Myers Squibb, Celgene and Novartis. AH is an employee of and holds stocks/shares in GlaxoSmithKline and is a non-executive director and holds stocks in Imugene. NL has received research funding from GlaxoSmithKline; RP has received honoraria from Janssen, Takeda, Celgene, and Amgen, and travel support to attend meetings from Janssen, Takeda, and Celgene. PGR is a consultant for, and has received research funding from, Celgene, Takeda, and Jazz Pharmaceuticals, and is a member of the board of directors/advisory committee for Celgene, Jazz Pharmaceuticals, Janssen, and Millennium. HJS has received honoraria from Janssen, Celgene, and Amgen. ST is a consultant for and has received honoraria from Amgen and Celgene; has received honoraria from Takeda and AbbVie; is a consultant for Novartis; and has received research support from Janssen. PMV is a consultant for Amgen, Celgene, Janssen, Bristol-Myers Squibb, Novartis, Takeda, and Teneo-Bio, and has participated in speakers' bureaux for Amgen, Celgene, and Janssen. KY is a consultant for Autolus, has received honoraria from Autolus, Amgen, Janssen, and Celgene, and has received research funding from Amgen, Janssen, Celgene, and Chugai. DJA, JBO, MMG, and ZH are employees of and hold stocks/shares in GlaxoSmithKline. SL was an employee of GlaxoSmithKline at the time of study conduct and holds stocks/shares in GlaxoSmithKline. BR and ENL declare no conflict of interest outside of the submitted work.

AUTHOR CONTRIBUTIONS

LDA contributed to acquisition of data; DJA contributed to data analysis and interpretation; ADC contributed to acquisition of data, data analysis and interpretation; MMG contributed to data analysis and interpretation; ZH contributed to data analysis and interpretation; AH contributed to data analysis and interpretation; SL contributed to data analysis and interpretation; NL contributed to acquisition of data, data analysis and interpretation; ENL contributed to acquisition of data, data analysis and interpretation; JBO contributed to study design, data analysis and interpretation; RP contributed to acquisition of data, data analysis and interpretation; BR contributed to acquisition of data, data analysis and interpretation; PGR contributed to acquisition of data, data analysis and interpretation; HJS contributed to acquisition of data; ST contributed to study design, acquisition of data, data analysis and interpretation; PMV contributed to study design and acquisition of data; KY contributed to study design and acquisition of data. All authors were involved at each stage of manuscript preparation and approved the final version.

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TABLES

Table 1. Patient baseline characteristics and disposition (Part 2)

Characteristic	n=35
Age, median (range), years	60 (46–75)
Sex, male / female, n (%)	17 (49) / 18 (51)
Disease stage at diagnosis[*] I / II / III / unknown, %	9 (26) /5 (14) /5 (14) / 16 (46)
Myeloma light chain, n (%)	
Kappa light chain	25 (71)
Lambda light chain	10 (29)
Myeloma immunoglobulin, n (%)	
IgA	8 (23)
IgG	22 (63)
IgM	1 (3)
Other	4 (11)
Genetics, n (%)[†]	
del13	5 (14)
del17p13	6 (17)
t(11:14)	2 (6)
t(4:14)	3 (9)
t(14:16)	1 (3)
+1q21	3 (9)
Other	15 (43)
Missing	11 (31)

Prior therapies, n (%)	
Received ≥5 lines of therapy	20 (57)
Proteasome inhibitors, received / refractory	35 (100) / 34 (97)
Immunomodulatory drugs, received / refractory	35 (100) / 32 (91)
Pomalidomide, received / refractory	21 (60) / 20 (57)
Daratumumab, received / refractory[‡]	14 (40) / 13 (37)
Carfilzomib, received / refractory	28 (80) / 26 (74)
Patient disposition, n (%)	
Completed study	9 (26)
Died	3 (9)
Ongoing on study	22 (63)
On treatment	17 (49)
In follow-up	5 (14)
Withdrawn from study	1 (3)
Withdrew consent	1 (3)
Lost to follow-up	0
Discontinued treatment	18 (51)
Disease progression	15 (43)
Completion of treatment	0
Adverse event	2 (6)
Investigator discretion	0
Patient decision	1 (3)

[*]Assessed using the International Staging System classification[15]; sum of categories <100% due to rounding.

[†]Multiple categories per patient possible; total may add to more than 100%; assessed using fluorescence in situ hybridisation.

‡Thirty-four percent of patients had prior daratumumab and were refractory to both immunomodulatory drugs and proteasome inhibitors.

Lactate dehydrogenase data at screening are not available.

Table 2. All adverse events (Grade 3, 4 and 5) by percentage and Grade 1 or 2 events occurring in ≥10% of patients for Part 2 and Parts 1 and 2 overall

Preferred Term, n (%)	**Part 2 (n=35)**				**Parts 1 and 2 overall (n=73)**			
Grade	**1–2***	**3**	**4**	**5**	**1–2***	**3**	**4**	**5**
Vision blurred	16 (46)				26 (36)	1 (1)		
Dry eye	11 (31)	1 (3)			19 (26)	2 (3)		
Cough	9 (26)				13 (18)			
Aspartate aminotransferase increased	8 (23)	2 (6)			16 (22)	2 (3)		
Chills	8 (23)				17 (23)			
Nausea	8 (23)				26 (36)			
Photophobia	8 (23)				12 (16)			
Pyrexia	8 (23)				16 (22)			
Thrombocytopenia†	8 (23)	9 (26)	3 (9)		11 (15)	18 (25)	7 (10)	
Fatigue	7 (20)				23 (32)	1 (1)		
Alanine aminotransferase increased	5 (14)				7 (10)			
Anaemia	5 (14)	5 (14)			10 (14)	11 (15)		

Back pain	5 (14)	1 (3)			10 (14)	1 (1)		
Decreased appetite	5 (14)				7 (10)			
Diarrhoea	5 (14)	1 (3)			8 (11)	2 (3)		
Headache	5 (14)				11 (15)			
Sinusitis	5 (14)				6 (8)			
Upper respiratory tract infection	5 (14)				11 (15)			
Arthralgia	4 (11)				9 (12)	1 (1)		
Constipation	4 (11)				7 (10)			
Lacrimation increased	4 (11)				4 (5)			
Dyspnoea	3 (9)	1 (3)			4 (5)	1 (1)		
Epistaxis	3 (9)				9 (12)			
Hypercalcaemia	3 (9)				6 (8)	3 (4)		
Lymphocyte count decreased	3 (9)				4 (5)		2 (3)	
Musculoskeletal chest pain	3 (9)				6 (8)	1 (1)		
Pain in extremity	3 (9)				8 (11)			

Gamma-glutamyl transferase increased	2 (6)	2 (6)			3 (4)	3 (4)		
Infusion-related reaction‡	2 (6)	2 (6)			4 (5)	2 (3)		
Lung infection	2 (6)	1 (3)			2 (3)	1 (1)		
Urinary tract infection	2 (6)	1 (3)			2 (3)	1 (1)		
Vomiting	2 (6)				5 (7)	1 (1)		
Neutrophil count decreased		2 (6)			2 (3)	3 (4)		
Visual acuity tests abnormal		1 (3)				1 (1)		
Keratitis	1 (3)	2 (6)			2 (3)	2 (3)		
Eye pain	1 (3)	1 (3)			2 (3)	1 (1)		
Eye disorder		1 (3)				1 (1)		
Retinal detachment		1 (3)				1 (1)		
Limbal stem cell deficiency						1 (1)		
Haematuria	1 (3)	1 (3)			2 (3)	1 (1)		
Hyperkalaemia	1 (3)				1 (1)	1 (1)		

Hyperuricaemia	1 (3)				1 (1)		1 (1)	
Hypokalaemia	1 (3)	2 (6)			1 (1)	3 (4)		
Hyponatraemia	1 (3)				4 (5)	2 (3)		
Hypotension	1 (3)				2 (3)	1 (1)		
Influenza	1 (3)				2 (3)	1 (1)		
Pain	1 (3)				2 (3)	1 (1)		
Pneumonia	1 (3)	1 (3)			2 (3)	2 (3)		
Appendicitis		1 (3)				1 (1)		
Bacteraemia			1 (3)				1 (1)	
Cellulitis		1 (3)				1 (1)		
Cholecystitis infective			1 (3)				1 (1)	
Deep vein thrombosis		1 (3)			1 (1)	1 (1)		
Encephalopathy		1 (3)				1 (1)		
Fall		1 (3)				1 (1)		
Hyperviscosity syndrome						1 (1)		

Hypophosphataemia						1 (1)		
Neutropenia		1 (3)	1 (3)		1 (1)	4 (5)	2 (3)	
Pericardial effusion			1 (3)				1 (1)	
Spinal cord compression						1 (1)		
Spinal cord injury thoracic						1 (1)		
Syncope						1 (1)		

*Grade 1 or Grade 2 events occurring in 10% of patients.

†Grouped term includes thrombocytopenia and platelet count decreased.

‡In Part 2, 8 (23%) patients had infusion-related reactions (as defined by a grouped term, including the preferred term infusion-related reaction); per protocol, premedication was not allowed for the first infusion.

FIGURE LEGENDS

Figure 1. CONSORT diagram
(A) Part 1 (Dose Escalation) and (B) Part 2 (Expansion Cohort)

Figure 2. Best responses to GSK2857916 (Part 2; 3·4 mg/kg dose)
(A) Maximum percentage change of serum/urine M-protein or free light chain as compared with baseline values. For patients with measurable serum M-protein, serum values are depicted; for patients who are followed by urine M-protein, the urine values are depicted; and for patients who did not have measurable serum or urine M-protein and were followed by free light chains, the values for free light chain are depicted. (B) Forest plot of overall response rate by patient subgroup (Part 2). Patients with any of the following genetic abnormalities were considered high risk: t(4:14), del17p, t(14:16).

Figure 3. Response durations and effect of dose modifications

(A) Duration of study treatment by response in Part 2 (3·4 mg/kg dose). Treatment duration counts the time difference between first dosing date and dosing end date without accounting for dosing interruptions. Triangles indicate ongoing patients. (B) Dose modifications in responding patients in Part 2. For each of the 21 responding patients, indicated in green font is initial response (PR or better); blue font, best response; red font, progressive disease; the numbers indicate dose for each infusion. CR: complete response, MR: minimal response, NE: not evaluable, PD: progressive disease, PR: partial response, sCR: stringent complete response, SD: stable disease, VGPR: very good partial response.

Figure 4. Kaplan–Meier curves for progression-free survival and duration of response

Progression-free survival (A) and duration of response (B) from Part 2 (dose expansion phase; 3·4 mg/kg dose) are shown. The median progression-free survival was 7·9 months and the median duration of response was not estimable. Tick marks indicate censored data.