Abbreviated Clinical Study Report Addendum 1 Synopsis	
Drug Substance	MEDI2228
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A Phase 1, Open-label Study to Evaluate the Safety, Pharmacokinetics, Immunogenicity, and Preliminary Efficacy of MEDI2228 in Subjects with Relapsed/Refractory Multiple Myeloma

Study dates: First patient enrolled: 08 May 2018
Last subject last visit: 21 March 2022
The analyses presented in this report are based on a clinical data lock date of 06 May 2022

Phase of development: Clinical pharmacology (I)

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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

Study centres

This study was conducted at 10 study sites globally (Australia [1 site], Greece [1 site], and the United States of America [8 sites]).

Publications

American Society of Hematology (ASH); 62nd ASH annual meeting and exposition - oral and poster abstracts (session 653): Phase 1, first-in-human study of MEDI2228, a B-cell maturation antigen (BCMA)-targeted antibody drug conjugate (ADC) in patients with relapsed/refractory multiple myeloma (Kumar et al 2020).

Objectives and criteria for evaluation

The objectives and endpoints of this study are summarized in Table S1.

Table S1 Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability, describe the DLTs, determine the MTD, or MAD, and RP2D for further evaluation of MEDI2228 in adult subjects with R/R MM.	• Incidence of AEs, SAEs, and DLTs. • Changes from baseline in laboratory parameters, vital signs, and ECG results.
Secondary	
• To evaluate the preliminary efficacy of MEDI2228 in adult subjects with R/R MM.	• Objective response, clinical benefit, DoR, PFS, and OS. • The IMWG consensus criteria for response and MRD assessment in MM will be used for disease assessment (Kumar et al 2016[a]).
• To describe the PK of MEDI2228 in adult subjects with R/R MM.	• Individual subject MEDI2228 concentrations (including MEDI2228 ADC, total antibody, and free warhead) in plasma at different time points after MEDI2228 administration. • Pharmacokinetic parameters that may have been calculated based on these data included, but were not limited to C_{max}, AUC, CL, and $t_{1/2}$.
• To determine the immunogenicity of MEDI2228 in adult subjects with R/R MM.	• The number and percentage of subjects who develop ADAs.

[a] Kumar S, Paiva B, Anderson Kc, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e46.

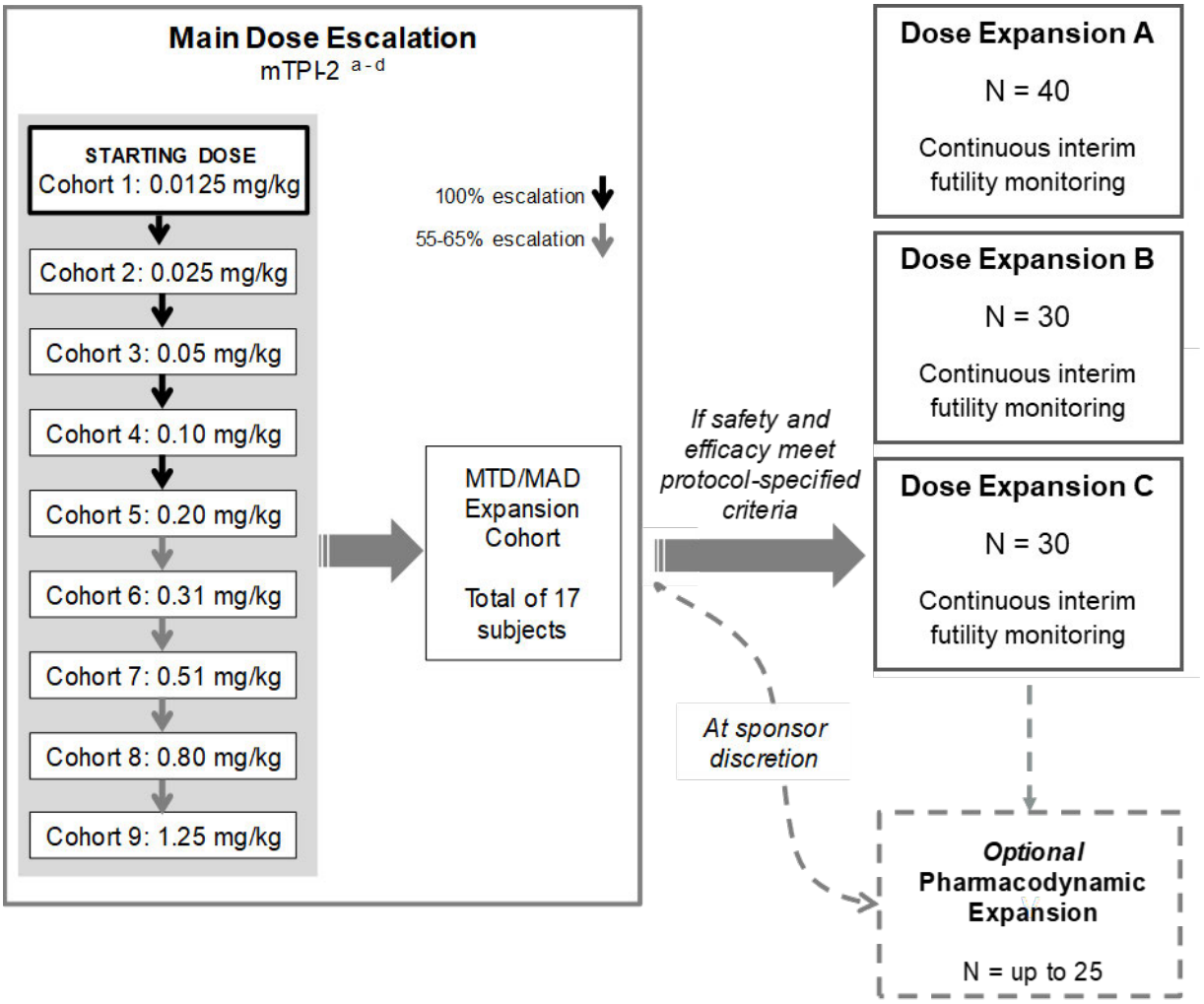
ADA, anti-drug antibody; ADC, antibody drug conjugate; AE, adverse event; AUC, area under the concentration-time curve; CL, clearance; C_{max}, maximum observed concentration; DLT, dose-limiting toxicity; DoR, duration of response; ECG, electrocardiogram; IMWG, International Myeloma Working Group; MAD, maximum administered dose; MM, multiple myeloma; MRD, minimal residual disease; MTD, maximum tolerated dose; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RP2D, recommended Phase 2 dose; R/R MM, relapsed/refractory multiple myeloma as defined for the study population (Section 1.4 of the CSP); SAE, serious adverse event; $t_{1/2}$, terminal half-life.

Study design

This was a first time in humans Phase I, open-label, dose-escalation and dose-expansion study to evaluate the safety, pharmacokinetics (PK), pharmacodynamics, immunogenicity, and preliminary efficacy of single agent MEDI2228 in adult patients with relapsed/refractory multiple myeloma (R/R MM). Up to 196 patients were planned to be enrolled in the study at approximately 30 participating sites globally.

During dose-escalation, single agent MEDI2228 was to be administered via intravenous (IV) infusion every 3 weeks (Q3W) to adult patients with R/R MM. The study aimed to evaluate up to 9 planned, sequentially ascending main dose levels (Figure S1). Intermediate dose levels with lower escalation increments (40% to 50% escalation increments prior to Cohort 5 and 25% to 30% escalation increments at higher doses) may have been evaluated based on emerging safety data (Figure S2).

Figure S1 Study Flow Diagram for Standard Dose Escalation and Dose Expansion



[a] Dose escalation was to follow the mTPI-2 algorithm (minimum 3 to 4 patients per cohort; maximum 12 patients per cohort).

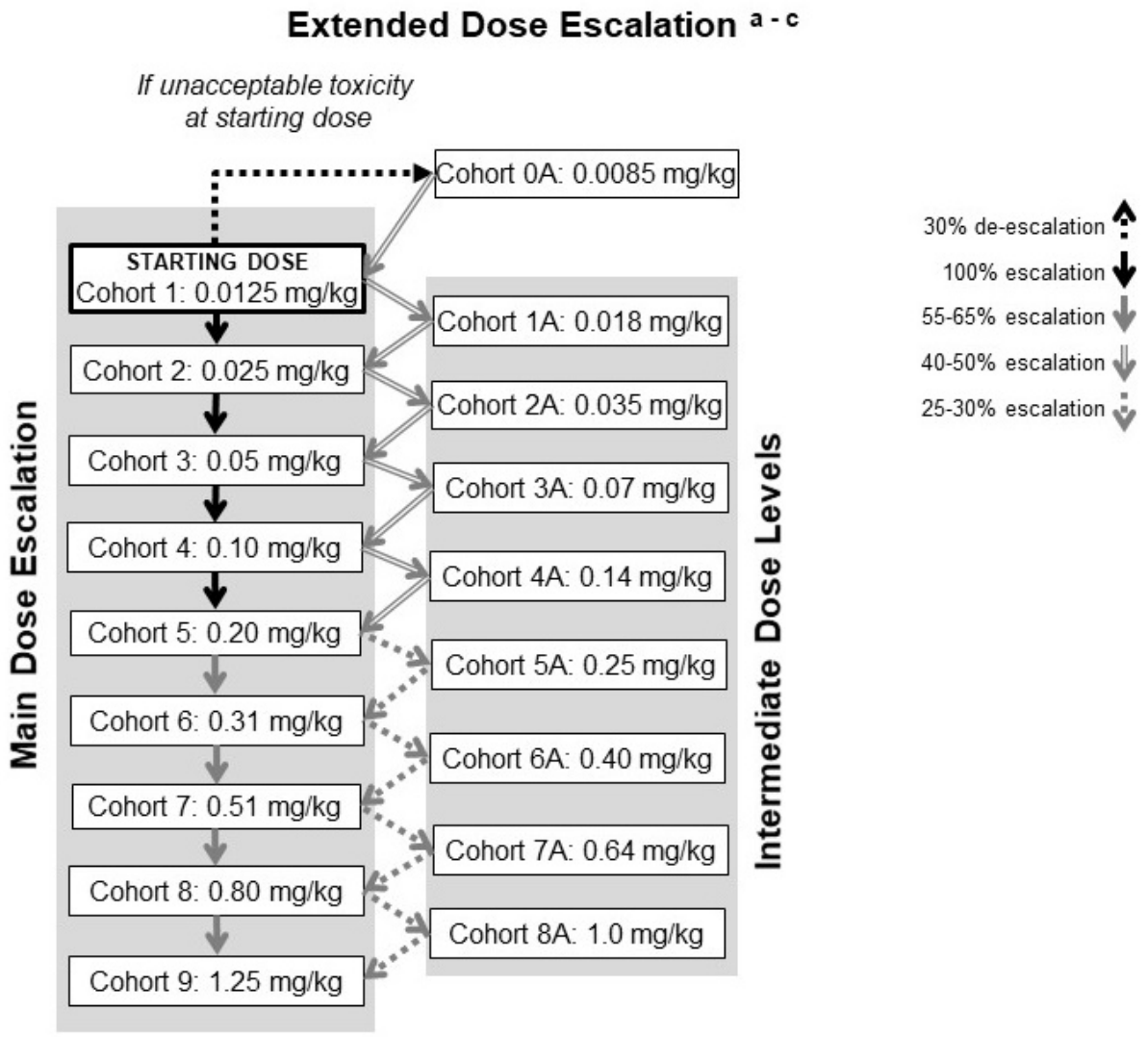
[b] Intermediate dose levels and dose levels below the planned starting dose may have been evaluated at the discretion of the DEC; see Figure S2 for additional details.

[c] Once a decision had been made to evaluate intermediate dose levels, further dose escalation should have included main and intermediate dose levels. Note: If an intermediate dose level was cleared without a DLT and the next main dose level was also cleared without a DLT, further dose escalation may have proceeded by main dose levels, at the discretion of the DEC.

[d] Additional patients up to a maximum of 18 patients (including patients dosed at the same dose level in dose-escalation) may have been enrolled to "back-fill" dose-escalation cohorts at any given dose level prior to determination of the MTD/MAD if (i) a decision to dose escalate to the next higher dose level was made and (ii) antitumour activity (minimal response or better by IMWG criteria) was observed at the given dose level.

DEC, Dose Escalation Committee; DLT, dose-limiting toxicity; IMWG, International Myeloma Working Group; MAD, maximum administered dose; MTD, maximum tolerated dose; mTPI-2, modified toxicity probability interval 2; N, total number of patients.

Figure S2 Study Flow Diagram for Extended Dose-escalation Scheme: Main and Intermediate Dose Levels



[a] If unacceptable toxicity was encountered at the starting dose, one dose de-escalation level (0.0085 mg/kg) may have been evaluated at the discretion of the DEC.

[b] If the decision was to escalate at any dose level, dose escalation was to proceed to an intermediate dose level if any of the following occurred: (i) ≥ 1 Grade 2 or higher pleural effusion, pericardial effusion, ascites, or CLS event; (ii) > 1 DLT but mTPI-2 algorithm still indicated dose escalation; (iii) at the discretion of the DEC.

[c] Once a decision was made to evaluate intermediate dose levels, further dose escalation should have included main and intermediate dose levels. Note: If an intermediate dose level was cleared without a DLT and the next main dose level was also cleared without a DLT, further dose escalation may have proceeded by main dose levels alone, at the discretion of the DEC.

CLS, capillary leak syndrome; DEC, Dose Escalation Committee; DLT, dose-limiting toxicity; mTPI-2, modified toxicity probability interval 2.

The dose-expansion phase was initiated after the maximum tolerated dose (MTD) or maximum administered dose (MAD) had been determined in the dose-escalation phase.

- A total of 40 adult patients with R/R MM were to be enrolled in the dose-expansion Cohort A at the dose selected for evaluation in the dose-expansion phase; continuous interim monitoring was to be performed after every 5 patients were enrolled.
- A total of 30 adult patients with R/R MM were to be enrolled in the dose-expansion Cohort B at 0.14 mg/kg Q6W dosing schedule.
- A total of 30 adult patients with R/R MM were to be enrolled in the dose-expansion Cohort C at 0.14 mg/kg Q3W for 2 cycles followed by 0.07 mg/kg Q6W dosing schedule.

Patients were followed for safety throughout the study. A study-specific Dose Escalation Committee provided ongoing safety surveillance of the study, with regularly scheduled reviews of safety, PK, and other relevant data. This committee could have met at other time points to review data (eg, in response to adverse events [AEs] assessed as medically relevant by the sponsor medical monitor). This committee were responsible for making recommendations for dose escalation or dose de-escalation decisions, and making recommendations regarding further conduct of the study, including selection of the recommended Phase II dose (RP2D), pausing enrolment, pausing dosing of enrolled patients, or dose de-escalation of enrolled patients (refer to Section 3.1.3 of the clinical study protocol [CSP]). The sponsor could halt or terminate the study at any time during dose escalation or dose expansion, based on emerging safety and efficacy data, or due to any other reason(s).

The information generated by this study was intended to inform decision-making regarding MEDI2228 as monotherapy or combination therapy in later-phase clinical studies. Per the study design, enrolled patients were planned to receive 1 of 3 dose and schedule regimens: MEDI2228 Q3W (dose-escalation and dose-expansion Cohort A), MEDI2228 every 6 weeks (Q6W; dose-expansion Cohort B), and MEDI2228 Q3W × 2 cycles followed by Q6W (dose-expansion Cohort C). However, the sponsor made the decision to terminate the study early following ongoing safety observations based on data cut on 15 January 2021, which showed a similar incidence of eye toxicity events (photophobia) in both Cohort A (MEDI2228 Q3W) and Cohort B (MEDI2228 Q6W) dose and schedule regimens. At the time of study termination (09 March 2021), patients had been fully enrolled in Cohort A and partially enrolled in Cohort B; no patients were enrolled in Cohort C.

Target population and sample size

Adult patients (aged ≥ 18 years) with a confirmed diagnosis of MM (per International Myeloma Working Group [IMWG] criteria) requiring systemic therapy; IMWG criteria for measurable disease was defined as at least one of the following: serum M-protein ≥ 0.5 g/dL, urine M-protein ≥ 200 mg/24 hours, and/or serum-free light chain (FLC) assay level ≥ 10 mg/dL (provided serum FLC ratio was abnormal). Patients were to have confirmed

relapsed/refractory (defined by IMWG consensus recommendations) and have exhausted standard-of-care regimens with proven clinical benefit (including proteasome inhibitors [PIs], immunomodulatory drugs [IMIDs], and monoclonal antibodies [mAbs]) and were to be ineligible for post-autologous stem cell transplant. Patients must have had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1 and were to consent to and undergo pre-treatment (baseline) fresh bone marrow aspirate and biopsy collection. Prior to being dosed with MEDI2228 on Cycle 1 Day 1, all prior treatment-related non-haematological toxicities must have been ≤ Grade 1 at the time of enrolment (except for alopecia and neuropathy); at least 7 days must have elapsed following corticosteroid therapy or plasmapheresis for MM; at least 14 days must have elapsed following palliative radiation therapy and treatment with anti-MM therapies given continuously or on a weekly basis with limited potential for delayed toxicity; at least 21 days must have elapsed following mAb treatment of MM.

Up to approximately 196 patients may have been enrolled in the study: up to approximately 71 patients in dose escalation (assuming 9 dose cohorts, 6 patients in the average/cohort, plus the 17 patient MTD/MAD expansion cohort), and up to approximately 100 patients in dose expansion (up to approximately 40 patients in dose expansion Cohort A, 30 patients in Cohort B, and 30 patients in Cohort C), plus the 25-patient optional pharmacodynamic cohort). Additional patients may have been required if additional cohorts or dosing schedules were explored.

The sample size of 40 patients for the dose-expansion Cohort A was primarily chosen to obtain a preliminary assessment of antitumour activity with a certain degree of precision. The sample size of 30 patients for dose-expansion Cohort B and Cohort C were to provide approximately 80% power to detect an objective response rate (ORR) difference of 20% at 2-sided significance level of 0.2, assuming the target ORR was 50% (ie, maintaining the observed ORR from dose-expansion Cohort A) and the historical control ORR is around 30% (Lonial et al 2020).

Investigational product: dosage, mode of administration and batch numbers

AstraZeneca provided the investigators with investigational product (IP) and IV bag protectant using designated distribution centres.

Table S2 Details of Study Treatments

Investigational Product	Manufacturer	Concentration and Formulation Supplied	Lot Numbers
MEDI2228	MedImmune	Supplied as a vialed lyophilized powder containing 6.0 mg (nominal) MEDI2228. When reconstituted with 3.2 mL of sWFI, the solution contains 2 mg/mL MEDI2228, 20 mM histidine/histidine-HCl, 4% (w/v) glycine, 2% (w/v) sucrose, and 0.02% (w/v) polysorbate 80, at pH 6.0. Administered intravenously.	170059; DOM 17 September 2017 190017; DOM 07 May 2019
IVBP	MedImmune	Supplied as a 1.0 mL (nominal) sterile liquid solution containing 25 mM sodium citrate dihydrate/citric acid, 0.65% (w/v) polysorbate 80, pH 6.0 in a 3 mL vial. Administered intravenously.	C10064; DOM 20 August 2014 HC0250; DOM 04 April 2016 KC0263; DOM 27 March 2018

DOM, date of manufacture; HCl, hydrochloride; IVBP, intravenous bag protectant; sWFI, sterile water for injection; w/v, weight/volume.

Duration of treatment

Patients from either the dose-escalation or dose-expansion phase may have received MEDI2228 for a maximum of 2 years. Patients who continued to demonstrate clinical benefit after this 2-year treatment period or at the time the study was terminated by the sponsor were eligible to receive MEDI2228 via the potential options outlined in Section 3.1.2 of the CSP.

Statistical methods

The As-treated population included patients who received at least one dose of study IP. Patients were analysed according to the treatment they actually received. The response evaluable population included patients from the As-treated population who had a baseline disease assessment (DA), had the opportunity to be followed for at least 3 weeks at the time of the data cut-off (DCO, ie, dosed at least 3 weeks prior to the time of the DCO), and either had at least one post-baseline DA and/or discontinued treatment due to death or disease progression prior to a post-baseline DA. The dose-limiting toxicity (DLT) evaluable population included all patients enrolled in the dose-escalation phase who received at least 1 dose of MEDI2228 and who completed the safety follow-up through the DLT evaluation period (defined as 21 days after the initiation of MEDI2228) or who experienced any DLT during the evaluation period.

The efficacy endpoints included best overall response (BOR); objective response (OR); clinical benefit; time to response (TTR); duration of response (DoR); progression-free survival

(PFS); and overall survival (OS). The primary analysis of efficacy endpoints was to be summarized based on the As-treated population. The analysis of BOR and OR based on response evaluable population was supportive. The analysis of all efficacy endpoints, except OS, was to be based on the disease response assessed by the investigators according to the IMWG Consensus Criteria for Response and Minimal Residual Disease Assessment in Multiple Myeloma.

Immunogenicity results were to be listed for each patient and summarized for the As-treated population. Number and percentage of patients in the following categories were to be provided: anti-drug antibody positive at baseline and/or post-baseline visits; persistent positive, defined as positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive at last post-baseline assessment; transient positive, defined as negative at last post-baseline assessment and positive at only one post-baseline assessment or at ≥ 2 post-baseline assessments (with <16 weeks between first and last positive).

MEDI2228 plasma concentration (including MEDI2228 ADC, total antibody, and free warhead) were to be summarized using the As-treated population by dose level/cohort and scheduled sampling time using descriptive statistics (n, n < lower limit of quantification [LLOQ], arithmetic mean, standard deviation [SD], median, minimum, maximum, coefficient of variation [CV%], geometric mean, geometric SD, geometric CV%).

All safety analyses were to be performed based on the As-treated population, unless otherwise specified. The MTD evaluation was to be based on the DLT Evaluable Population. The number and percentage of patients with DLTs were to be presented by dose level. Adverse events were to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 and the type, incidence, severity, and relationship to study investigational product was to be summarized. Specific AEs were to be counted once for each patient for calculating percentages. In addition, if the same AE occurred multiple times within a particular patient, the highest severity and relatedness observed was to be reported. All treatment-emergent AEs (TEAEs) (defined as events present at baseline that worsen in intensity after administration of study IP or events absent at baseline that emerge after administration of study IP) were to be summarized overall, as well as categorized by MedDRA system organ class and preferred term. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections (confirmed or suspected) were to be reported. Adverse events of special interest (AESIs) included but were not limited to hepatic function abnormality, infections, peripheral oedema without serosal effusions, serosal effusions with or without associated peripheral oedema, capillary leak syndrome, skin toxicity and ocular and periocular changes (including, but not limited to dry eye, periorbital oedema, photophobia, blepharitis, pruritus, corneal abnormalities, meibomian gland or lacrimal gland dysfunction).

Laboratory parameters were to be assessed at baseline as well as throughout the study. Frequencies of worst observed Grade 0 to 4 toxicity, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03, were to be presented for each laboratory parameter. The analysis was also to present worst grade observed and the rates of patients with Grade 3 to Grade 4 toxicity.

Vital signs were to be assessed at baseline and throughout the study. Descriptive statistics were to be provided for the vital sign measurements and changes from baseline to scheduled time of evaluation, and the maximum and minimum post-baseline values. Electrocardiogram (ECG) parameters were to be assessed at baseline as well as throughout the study. Abnormal ECG parameters were to be summarized using descriptive statistics; changes from baseline to scheduled time of evaluation and to the maximum post-baseline values were to be summarized. The ECOG PS was to be assessed at baseline as well as throughout the study and was to be summarized by cohort and study visit, including descriptive statistics for the value of the parameters and the changes from baseline.

The first interim analysis was to be performed starting with 17 patients at the MTD/MAD and was to include patients evaluated at the MTD/MAD dose level and patients in the MTD/MAD expansion cohort. After this initial interim analysis, during dose expansion, the subsequent interim analyses were to be performed after every 5 patients were enrolled.

The data analyses were conducted using the SAS® System (SAS Institute, Inc., Cary, NC, USA) Version 9.4. All analysis outputs were validated according to MedImmune SAS programming standards and MedImmune validation procedures.

Study population

This abbreviated clinical study report (aCSR) addendum includes safety and efficacy data for 107 patients (database lock [DBL] 06 May 2022). The first patient was enrolled into the study (ie, provided written informed consent) on 08 May 2018, and the first patient received treatment on 22 May 2018. At the time of DBL, no patients had completed treatment as defined in the CSP. At the time of DBL, all 107 (100%) patients had an end of study status recorded as either death (66 [61.7%] patients), withdrawal by patient (14 [13.1%] patients), lost to follow-up (7 [6.5%] patients), or other (20 [18.7%] patient). A total of 107 patients were enrolled at 10 study sites globally.

Of the 129 patients screened, 22 patients were screen failures and 107 patients received treatment with MEDI2228. All (100%) patients discontinued from study treatment; the most common reasons for discontinuation were AEs (48 [44.9%] patients) and progressive disease (43 [40.2%] patients). Other reasons reported for discontinuation of treatment were patient decision (6 [5.6%] patients), death (5 [4.7%] patients), investigator decision (3 [2.8%] patients), and clinical relapse and initiation of subsequent anticancer treatment

(1 [0.9%] patient each). The most commonly reported end-of-study status was death (66 [61.7%] patients); the only other end-of-study status reported for ≥ 10% of patients were withdrawal by patient (14 [13.1%] patients) and other (20 [18.7%] patients).

In Cohort A, 26 (63.4%) patients discontinued treatment due to AEs and 10 (24.4%) patients discontinued treatment due to disease progression. In Cohort B, 7 (28.0%) patients discontinued treatment due to AEs and 11 (44.0%) patients discontinued treatment due to disease progression.

Of note, the majority of patients (82 [76.6%] patients) were enrolled prior to the start of the coronavirus disease 2019 (COVID-19) pandemic (ie, before 11 March 2020); these 82 patients accounted for all patients in the following dose groups: 0.125 mg/kg Q3W, 0.025 mg/kg Q3W, 0.05 mg/kg Q3W, 0.10 mg/kg Q3W, 0.14 mg/kg Q3W (Cohort A), and 0.20 mg/kg Q3W. All 25 (100%) patients in Cohort B (0.14 mg/kg Q6W) were enrolled after the start of the COVID-19 pandemic. No patients in this study were affected by the COVID-19 pandemic.

Summary of efficacy results

- The majority of patients (29 [70.7%] patients) in Cohort A had OS, with a median OS of 12.9 months (95% confidence interval [CI]: 6.6, 16.6). Overall survival was 63.4% patients (95% CI: 57.1, 86.0) at 6 months, and 43.9% patients (95% CI: 34.3, 66.7) at 12 months.
- In Cohort B, 7 (28.0%) patients had OS, with a median OS of 15.8 months (95% CI: 8.7, not applicable [NA]). Overall survival was 68.0% patients (95% CI:64.8, 97.3) at 6 months, and 32.0% patients (95% CI: 38.4, 85.9) at 12 months.
- One (2.5%) patient in Cohort A achieved a stringent complete response (CR). No other patients in any of the other dose groups had a CR. In Cohort A, 9 (22.0%) patients had very good partial response (VGPR) and 13 (31.7%) patients had partial response (PR). In Cohort B, 2 (8.0%) patients had VGPR and 6 (24.0%) patients had PR.
- The ORR in Cohort A was 56.1% patients (95% CI: 39.7, 71.5). The ORR in Cohort B was 32.0% patients (95% CI: 14.9, 53.5).
- The median time to response was the same for Cohort A and Cohort B (2.1 months [95% CI for Cohort A: 0.7, 2.4; 95% CI for Cohort B: 1.4, 4.2]).
- The median DoR in Cohort A was 5.9 months (95% CI: 4.8, 8.5). The median DoR in Cohort B was 7.7 months (95% CI: 1.7, NA).
- The majority of patients (27 [65.9%] patients; 95% CI: 49.4, 79.9]) in Cohort A achieved clinical benefit. In Cohort B, 12 (48.0%) patients (95% CI: 27.8, 68.7) achieved clinical benefit.
- The majority of patients in Cohort A (28 [68.3%] patients) and Cohort B (14 [56.0%] patients) had PFS, with a median PFS of 6.6 months (95% CI: 3.7, 7.6) and 5.1 months (95% CI: 2.8, 9.0), respectively.
  - In Cohort A, PFS was 36.6% patients (95% CI: 36.4, 70.5) at 6 months, and 9.8% patients (95% CI: 5.1, 32.1) at 12 months.

- In Cohort B, PFS was 24.0% patients (95% CI: 19.1, 61.1) at 6 months; and 4.0% patients (95% CI: 4.0, 45.4). at 12 months.

Summary of pharmacokinetic results

- The PK profile of MEDI2228 ADC was similar to that of total antibody. Over the dose levels of 0.0125 mg/kg to 0.20 mg/kg after the first IV infusion dose of MEDI2228 Q3W, the geometric mean PK exposures (C_{max}, AUC_{last}, and $AUC_{[0-21]}$) of MEDI2228 ADC and total antibody appeared to increase in a dose-proportional manner. The geometric mean C_{trough} of MEDI2228 and total antibody appeared to increase in a dose-proportional manner at dose levels ≥ 0.05 mg/kg.
- No significant accumulation was observed. Geometric mean accumulations of MEDI2228 ADC ratios of geometric mean C_{max} on Day 64 or Day 85 versus C_{max} after the first dose, and C_{trough} on Day 64 or Day 85 versus C_{trough} after the first dose ranged from 1.190 to 1.247 for Rac C_{max} and from 1.459 to 1.705 for Rac C_{trough}, respectively. Geometric mean accumulations of total antibody ranged from 1.125 to 1.346 for Rac C_{max} and from 1.303 to 1.824 for Rac C_{trough}, respectively.
- The PK parameters (C_{max}, t_{max}, AUC_{last}, and $t_{½}\lambda_z$) of MEDI2228 ADC and total antibody were similar between Q3W and Q6W dose regimens at the dose level of 0.14 mg/kg MEDI2228.
- The majority of free warhead PK were below the limit of quantification (< 20 pg/mL), indicating good plasma stability of MEDI2228 ADC.
- Overall, < 10% of patients treated with MEDI2228 had positive ADA results at either baseline (9 [8.4%] patients) or post-baseline (8 [8.2%] patients).
  - In Cohort A, no patients were ADA positive at baseline; 1 (2.9%) patient was ADA persistent positive post-baseline.
  - In Cohort B, 4 (16.0%) patients were ADA positive at baseline and 3 (13.0%) patients were ADA persistent positive post-baseline.

Summary of safety results

- Overall, 2 (1.9%) patients (both in the 0.20 mg/kg Q3W dose group) each had single DLTs of thrombocytopenia (Grade 2 and Grade 3 TEAEs); both TEAEs were nonserious, were related to MEDI2228, and had outcomes reported as recovered/resolved. The MTD of MEDI2228 was 0.14 mg/kg, which resulted in the RP2D of 0.14 mg/kg.
- Overall, the median duration of exposure of MEDI2228 across all dose levels was 2.73 months (range: 0.1-13.85 months) and the median number of cycles was 3 cycles (range: 1-18 cycles).
- Overall, the most frequently reported (occurring in ≥ 40% of patients) TEAEs were fatigue (48 [44.9%] patients), and anaemia and photophobia (47 [43.9%] patients, each).
  - Frequently reported (occurring in ≥ 40% of patients) TEAEs in Cohort A were photophobia (25 [61.0%] patients), thrombocytopenia (18 [43.9%] patients), and

anaemia (17 [41.5%] patients); and in Cohort B were anaemia and fatigue (11 [44.0%] patients, each), and photophobia (10 [40.0%] patients).

- Overall, 90 (84.1%) patients had MEDI2228-related TEAEs. Frequently reported (occurring in ≥ 15% of patients) MEDI2228-related TEAEs were photophobia (47 [43.9%] patients), rash (31 [29.0%] patients), thrombocytopenia (21 [19.6%] patients), pleural effusion (17 [15.9%] patients), and anaemia and dry eye (16 [15.0%] patients, each). MEDI2228-related TEAEs occurring in ≥ 5% patients that resulted in treatment discontinuation were photophobia (15 [14.0%] patients) and pleural effusion (6 [5.6%] patients).
  - Frequently reported (occurring in ≥ 30% of patients) MEDI2228-related TEAEs in Cohort A and Cohort B were photophobia (25 [61.0%] patients and 10 [40.0%] patients, respectively) and rash (13 [31.7%] patients and 8 [32.0%] patients, respectively).
- Overall, the majority of patients (88 [82.2%] patients) had at least one TEAE of Grade 3 to Grade 4 severity. Frequently reported (occurring in ≥ 15% patients overall) TEAEs of Grade 3 to Grade 4 severity were anaemia (33 [30.8%] patients), thrombocytopenia (28 [26.2%] patients), gamma-glutamyltransferase increased (19 [17.8%] patients), and neutropenia (16 [15.0%] patients).
  - Frequently reported (occurring in ≥ 15% patients) TEAEs of Grade 3 to Grade 4 severity in Cohort A were thrombocytopenia (15 [36.6%] patients), gamma-glutamyltransferase increased (11 [26.8%] patients), neutropenia (8 [19.5%] patients), and photophobia (7 [17.1%] patients); and in Cohort B were anaemia (11 [44.0%] patients), thrombocytopenia (5 [20.0%] patients), and gamma-glutamyltransferase increased (4 [16.0%] patients).
- Overall, 53 (49.5%) patients had at least one AESI. Of these patients, 40 (37.4%) had MEDI2228-related AESIs and 12 (11.2%) patients had at least one MEDI2228-related AESI of Grade 3 to Grade 4 severity.
- Overall, 5 (4.7%) patients had TEAEs with fatal outcomes.
  - In Cohort A, fatal TEAEs of septic shock and ovarian cancer were each reported for 1 (2.4%) patient.
  - In Cohort B, fatal TEAEs of sudden cardiac death and encephalopathy were each reported for 1 (4.0%) patient. One (4.0%) patient had a fatal TEAE for which the cause could not be determined (reported by the investigator as death [unknown cause]); no autopsy was performed for this patient. None of these fatal TEAEs were related to MEDI2228 and no deaths occurred while the patients were on treatment.
- At the time of DBL (06 May 2022), 66 (61.7%) patients had died; the majority of whom (54 [50.5%] patients) died as a result of their multiple myeloma. Twenty-one (19.6%) patients died of their multiple myeloma within 90 days of the last dose of MEDI2228 and 1 (0.9%) patient died of their multiple myeloma within 30 days of the last dose of MEDI2228. For 12 (11.2%) patients, the cause of death was categorized as other; 3 deaths

categorized as other were within 90 days of the last dose of MEDI2228 and 1 death categorized as other was within 30 days of the last dose of MEDI2228.

- Overall, 51 (47.7%) patients had at least one serious TEAE. The proportion of patients who had at least one serious TEAE was similar between Cohort A (51.2%) and Cohort B (56.0%). Overall, 18 (16.8%) patients had MEDI2228-related serious TEAEs. The proportion of patients who had MEDI2228-related serious TEAEs was similar between Cohort A (19.5%) and Cohort B (20.0%).
  - In Cohort A, the only MEDI2228-related serious TEAEs occurring in ≥ 5% of patients was pleural effusion (3 [7.3%] patients). In Cohort B, the only MEDI2228-related serious TEAE occurring in ≥ 5% of patients was pericardial effusion (3 [12.0%] patients.
- Five (4.7%) patients had Grade 4 serious TEAEs: in Cohort A, thrombocytopenia and fatigue were each reported for 1 (2.4%) patient; and in Cohort B, cardiac tamponade, pericardial effusion, incarcerated incisional hernia, and metabolic encephalopathy were each reported for 1 (4.0%) patient.
- Overall, 48 (44.9%) patients had TEAEs resulting in discontinuation of MEDI2228. Frequently reported (occurring in ≥ 5% patients overall) TEAEs resulting in discontinuation of MEDI2228 were photophobia (15 [14.0%] patients), pleural effusion and gamma-glutamyltransferase increased (7 [6.5%] patients each), and thrombocytopenia (6 [5.6%] patients).
  - In Cohort A, TEAEs resulting in discontinuation of MEDI2228 occurring in ≥ 5% of patients were photophobia (11 [26.8%] patients), gamma-glutamyltransferase increased (5 [12.2%] patients), and eye irritation and pleural effusion (3 [7.3%] patients, each). In Cohort B, the only TEAE resulting in discontinuation of MEDI2228 occurring in ≥ 5% of patients was thrombocytopenia (2 [8.0%] patients).
- In general, there were no clinically meaningful changes from baseline in clinical laboratory data, vital signs, ECG results, ECOG PS, or other physical findings.

Conclusions

- MEDI2228 is a B-cell maturation antigen (BCMA)-targeted antibody drug conjugate (ADC) that demonstrated clinically meaningful efficacy across all dose levels explored in this study in a heavily pre-treated population with multiple myeloma that was R/R post-PI, IMID, and mAb therapies, with an ORR of 56.1% patients (95% CI: 39.7, 71.5) and a median OS of 12.9 months (95% CI: 6.6, 16.6) in the 0.14 mg/kg Q3W in the 0.14 mg/kg Q3W dose regimen.
- The most frequently reported TEAEs were fatigue, anaemia, and photophobia.
  The sponsor terminated the study following ongoing safety observations based on a data cut on 15 January 2021, which showed a prevalence of eye toxicity events (photophobia) following Q3W and Q6W MEDI2228 administration.

SCOPE OF THE ADDENDUM

At the time of publishing of the main aCSR (18 November 2021; DCO: 08 July 2021), 3 (2.8%) patients, all of which were in Cohort B, were ongoing on treatment, 17 (15.9%) patients (5 patients in Cohort A, 8 patients in Cohort B, and 4 patients in the 0.10 mg/kg Q3W dose group) were in survival follow-up, and 7 (6.5%) patients (3 patients in Cohort A and 4 patients in Cohort B) were in long-term follow-up. At the time of DBL (06 May 2022), all patients had discontinued from treatment. This aCSR addendum presents the final disposition, efficacy, and safety results for Study D7900C00001. No updates have been made to the PK or immunogenicity results in this addendum. For PK and immunogenicity results, please refer to Section 11.2 and Section 11.5 of the main aCSR, respectively.

The DBL of 06 May 2022 has provided longer-term efficacy and safety follow-up data than those presented in the main aCSR (DCO: 08 July 2021). Whilst the overall conclusions remain the same, efficacy results have changed as follows:

- The number of patients in Cohort A with OS increased from 63.4% to 70.7%; the median OS remained at 12.9 months (95% CI: 6.6, 16.6).
- The number of patients in Cohort B with OS increased from 12.0% to 28.0%; the median OS increased from 12.0 months (95% CI: 12.0, NA) to 15.8 months (95% CI: 8.7, NA).
- The ORR in Cohort A decreased from 61.0% patients (95% CI: 44.5, 75.8) to 56.1% patients (95% CI: 39.7, 71.5).
- The ORR in Cohort B increased from 28.0% patients (95% CI: 12.1, 49.4) to 32.0% patients (95% CI: 14.9, 53.5).
- The number of patients in Cohort A with PFS remained at 68.3%; the median PFS remained at 6.6 months (95% CI: 3.7, 7.6).
- The number of patients in Cohort B with PFS increased from 52.0% to 56.0%; the median PFS remained at 5.1 months (95% CI: 2.8, 9.0).