



(51) International Patent Classification:

A61K 39/395 (2006.01) C07K 16/30 (2006.01)

A61K 47/68 (2017.01) C07K 19/00 (2006.01)

A61P 35/00 (2006.01) C12N 15/62 (2006.01)

(21) International Application Number:

PCT/IB2021/060187

(22) International Filing Date:

03 November 2021 (03.11.2021)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/109,805 04 November 2020 (04.11.2020) US

(71) Applicant: MEDIMMUNE, LLC [US/US]; One MedImmune Way, Gaithersburg, Maryland 20878 (US).

(72) Inventors: WALCOTT, Farzana; MedImmune, LLC, One MedImmune Way, Gaithersburg, Maryland 20878 (US). YAO, Nai Shun; MedImmune, LLC, One MedImmune Way, Gaithersburg, Maryland 20878 (US).

(74) Agent: REHFUSS, Patrick; c/o AstraZeneca Pharmaceuticals LP, One MedImmune Way, Gaithersburg, Maryland 20878 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))
- with sequence listing part of description (Rule 5.2(a))
- in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE

(54) Title: TREATMENT METHODS USING ANTI-BCMA ANTIBODY-DRUG CONJUGATES

(57) Abstract: This disclosure relates to methods of treating cancers in a human patient (e.g., Multiple myeloma (MM)) comprising administration of an antibody-drug conjugate (ADC) comprising a monoclonal antibody, or an antigen-binding fragment thereof, directed against B-cell maturation antigen (BCMA) conjugated to a cytotoxin. The disclosure also provides compositions comprising the antibody-drug conjugate and methods of killing multiple myeloma cells (including multiple myeloma stems cells) that express BCMA by contacting multiple myeloma cells with the ADC.



TREATMENT METHODS USING ANTI-BCMA ANTIBODY-DRUG CONJUGATES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of U.S. Provisional Patent Application No. 63/109,805, filed November 4, 2020, which is incorporated by reference herein in its entirety for all purposes.

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0002] Incorporated by reference in its entirety herein is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: One 9,512 Byte ASCII (Text) file named “BCMA-200-WO-PCT_seq-listing,” created on November 1, 2021.

BACKGROUND

[0003] Multiple myeloma (MM) is a plasma cell malignancy which remains incurable despite of the recent emergence of multiple novel agents. Although current treatments are highly effective in controlling the disease and producing deep remissions, including molecular remissions, the disease invariably relapses after a period of time, requiring continued therapeutic intervention to maintain disease control (Kumar et al, 2017). As the disease relapses, it becomes increasingly refractory to the currently available drugs resulting in ever shorter remissions, with the vast majority of patients eventually succumbing to complications of relapsed, refractory disease.

[0004] B-cell maturation antigen (BCMA) is a tumor necrosis family receptor (TNFR) member expressed on cells of the B-cell lineage (Laabi et al., *Nucleic Acids Research*, 22(7): 1147-1154 (1994)). BCMA expression is highest on terminally differentiated B cells. BCMA is involved in mediating the survival of plasma cells for maintaining long-term humoral immunity.

The expression of BCMA has been linked to a number of cancers, autoimmune disorders, and infectious diseases. BCMA RNA has been detected universally in multiple myeloma cells, and BCMA protein has been detected on the surface of plasma cells from multiple myeloma patients by several investigators (see, e.g., Novak et al., *Blood*, 103(2): 689-694 (2004); Neri et al., *Clinical Cancer Research*, 73(19): 5903-5909 (2007); Bellucci et al., *Blood*, 105(10): 3945-3950 (2005); and Moreaux et al., *Blood*, 703(8): 3148-3157 (2004)). As such, BCMA has been investigated as a possible therapeutic target for multiple myeloma.

[0005] Treatment of multiple myeloma typically involves high-dose chemotherapy followed by hematopoietic stem cell transplantation (allogenic or autologous). However, a high rate of relapse is common in multiple myeloma patients that have undergone such treatment. Accordingly, there is a need for effective methods of treating multiple myeloma.

BRIEF SUMMARY

[0006] The present disclosure provides a method of treating Multiple Myeloma (MM) in a subject, the method comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an antibody-drug conjugate (ADC), wherein the ADC is directed against B-Cell Maturation Antigen (BCMA).

[0007] The present disclosure also provides a method of treating Relapsed/Refractory Multiple Myeloma (MM) in a subject, the method comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an antibody-drug conjugate (ADC), wherein the ADC is directed against B-Cell Maturation Antigen (BCMA).

[0008] The present disclosure also provides a method of killing multiple myeloma (MM) cells in a subject, the method comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an antibody-drug conjugate (ADC), wherein the ADC directed against B-Cell Maturation Antigen (BCMA).

[0009] The present disclosure also provides a method of increasing susceptibility Multiple Myeloma (MM) cells to Natural Killer (NK) cell-mediated killing in a subject in need thereof comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA).

- [0010] The present disclosure also provides a method of increasing CD38 expression in Multiple Myeloma (MM) cells in a subject in need thereof comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA).
- [0011] In some aspects of the present disclosure, the ADC comprises an antibody or antigen-binding fragment thereof that specifically binds to BCMA (anti-BCMA antibody or antigen-binding fragment thereof).
- [0012] In some aspects, the methods disclosed herein comprise administering to the subject about 0.0125 mg/kg, about 0.025 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.10 mg/kg, about 0.11 mg/kg, about 0.12 mg/kg, about 0.13 mg/kg, about 0.14 mg/kg, about 0.15 mg/kg, about 0.16 mg/kg, about 0.17 mg/kg, about 0.18 mg/kg, about 0.19 mg/kg, or about 0.20 mg/kg.
- [0013] In some aspects, the methods disclosed herein comprise administering about 0.14 mg/kg of the ADC to the subject.
- [0014] In some aspects, the methods disclosed herein comprise administering about 0.20 mg/kg of the ADC to the subject.
- [0015] In some aspects of the methods disclosed herein, one dose of ADC is administered to the subject once per treatment cycle. In some aspects, a treatment cycle is 28 days. In some aspects, a treatment cycle is about 4 weeks.
- [0016] In some aspects of the methods disclosed herein, the ADC is administered once every 3 weeks. In some aspects, the ADC is administered once every 6 weeks. In some aspects, the ADC is administered at a dose of about 0.14 mg/kg once every 3 weeks. In some aspects the ADC is administered at a dose of about 0.14 mg/kg once every 6 weeks.
- [0017] In some aspects of the methods disclosed herein, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds strongly to membrane-bound BCMA.
- [0018] In some aspects of the methods disclosed herein, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds weakly to monomeric (soluble) BCMA.
- [0019] In some aspects of the methods disclosed herein, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds to monomeric (soluble) BCMA with a binding affinity of about 60 nM, as measured by surface plasmon resonance. In some aspects, the

anti-BCMA antibody or antigen-binding fragment thereof binds to monomeric (soluble) BCMA with a binding affinity of 60.7 nM, as measured by surface plasmon resonance.

[0020] In some aspects of the methods disclosed herein, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds to cell-bound BCMA with a binding affinity of between about 2 nM and 4 nM, as measured by flow cytometry. In some aspects, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds to cell-bound BCMA with a binding affinity of about 3 nM, as measured by flow cytometry.

[0021] In some aspects of the methods disclosed herein, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof conjugated to a cytotoxin via a linker. In some aspects, the linker is a protease-cleavable linker. In some aspects, the cytotoxin is a pyrrolobenzodiazepine (PBD). In some aspects, the PBD is a DNA cross-linking PBD dimer.

[0022] In some aspects of the methods disclosed herein, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof, wherein the Fc effector function of the anti-BCMA antibody or antigen-binding fragment thereof is eliminated.

[0023] In some aspects of the methods disclosed herein, administration of the anti-BCMA antibody or antigen-binding fragment thereof does not result in significant epithelial changes in the cornea.

[0024] In some aspects of the methods disclosed herein, the methods further comprise measuring BCMA expression in plasma cells obtained from the subject. In some aspects the plasma cells are obtained from a bone marrow biopsy from the subject. In some aspects BCMA expression is assessed by immunohistochemistry (IHC). In some aspects the bone marrow biopsy contains $\geq 80\%$ CD138+ plasma cells that are BCMA+.

[0025] In some aspects of the methods disclosed herein, the antibody-drug conjugate (ADC), directed against B-Cell Maturation Antigen (BCMA) is administered to a cohort of subjects. In some aspects, the administration results in an overall response rate of at least 61%.

[0026] In some aspects of the methods disclosed herein, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity

determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6.

[0027] In some aspects, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof comprising a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 7 and/or a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 8.

[0028] In some aspects, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof comprising a full-length heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 9 and/or a full-length light chain (LC) comprising the amino acid sequence of SEQ ID NO: 10.

[0029] In some aspects, the ADC comprises a monoclonal anti-BCMA antibody or antigen-binding fragment thereof. In some aspects, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that is a full-length antibody. In some aspects, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that is an antigen binding fragment. In some aspects, the antigen binding fragment comprises a single chain Fv (scFv).

[0030] In some aspects of the methods disclosed herein, the subject is human. In some aspects, the administration is intravenous. In some aspects, the administration is intraperitoneal. In some aspects, the administration is subcutaneous.

[0031] Also provided herein is a method of treating Multiple Myeloma (MM) in a subject, the method comprising intravenously administering 0.14 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) every 3 weeks, wherein the ADC comprises: (a) an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6; (b) a protease-cleavable linker; and (c) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer.

[0032] Also provided herein is a method of treating Multiple Myeloma (MM) in a subject, the method comprising intravenously administering 0.14 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) every 6 weeks, wherein the ADC comprises: (a) an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6; (b) a protease-cleavable linker; and (c) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer.

[0033] Also provided herein is a method of treating Multiple Myeloma (MM) in a subject, the method comprising intravenously administering 0.14 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) every 3 weeks for 2 cycles, and then intravenously administering 0.07 mg/kg of the ADC every 6 weeks, wherein the ADC comprises: (a) an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6; (b) a protease-cleavable linker; and (c) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer.

[0034] Also provided herein is a method of treating Multiple Myeloma (MM) in a subject, the method comprising intravenously administering 0.10 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) every 3 weeks for at least 6 months, wherein the ADC comprises: (a) an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable

region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6; (b) a protease-cleavable linker; and (c) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer.

[0035] In some aspects of the methods disclosed herein, the subject has been pre-treated with daratumumab.

[0036] In some aspects of the methods disclosed herein, the administration results in a response in the subject for a duration of at least 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months.

[0037] In some aspects, the methods disclosed herein further comprise administration of one or more additional therapeutic agents. In some aspects, the additional therapeutic agent is Daratumumab. In some aspects, the additional therapeutic agents are Lenalidomide and dexamethasone. In some aspects, the ADC and the one or more additional therapeutic agents are administered simultaneously or sequentially.

[0038] Also provided herein is a method of treating Multiple Myeloma (MM) in a subject, the method comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA), wherein the ADC comprises: (a) an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6; (b) a protease-cleavable linker; and (c) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer, and wherein $\geq 80\%$ of bone marrow plasma cells obtained from the subject are CD138+ and BCMA+.

BRIEF DESCRIPTION OF THE DRAWINGS

- [0039] FIG. 1 shows the study design for the first in human dose-escalation and expansion study described herein.
- [0040] FIG. 2 shows efficacy of the anti-BCMA ADC at all dose levels (n=82). The Y-axis is the dosage, increasing from 0.0125 mg/kg to 0.20 mg/kg from top to bottom. The X-axis is the time patients were on the treatment (in days).
- [0041] FIG. 3 shows a concentration-time profile after the first dose of the anti-BCMA ADC. The key shows the dose tested in each cohort.
- [0042] FIG. 4 shows the duration of treatment and response for patients on the 0.14 mg/kg dose (n=41). Each bar on the Y-axis represents one patient. The X-axis is the time each patient was on the treatment.
- [0043] FIG. 5 shows expansion dose modifications and early and late responses in patients in the 0.14 mg/kg cohort (n=25/41 responders (ORR 61.0%)).
- [0044] FIG. 6 shows the durability of response signal at the 0.1 mg/kg dose level (n=18).

DETAILED DESCRIPTION

- [0045] The present disclosure provides an antibody-drug conjugate (ADC) comprising a monoclonal antibody, or an antigen-binding fragment thereof, directed against B-cell maturation antigen (BCMA) conjugated to a cytotoxin.

1. Definitions

- [0046] The term “antibody” (Ab) includes, without limitation, a glycoprotein immunoglobulin which binds specifically to an antigen and comprises at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds. Each H chain comprises a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region comprises three constant domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprises one constant domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed

complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL comprises three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (C1q) of the classical complement system. A heavy chain may have the C-terminal lysine or not. Unless specified otherwise herein, the amino acids in the variable regions are numbered using the Kabat numbering system and those in the constant regions are numbered using the EU system.

[0047] The term “monoclonal antibodies,” as used herein, refers to antibodies that are produced by a single clone of B-cells and bind to the same epitope. In contrast, the term “polyclonal antibodies” refers to a population of antibodies that are produced by different B-cells and bind to different epitopes of the same antigen. The term “antibody” includes, by way of example, monoclonal and polyclonal antibodies; chimeric and humanized antibodies; human or nonhuman antibodies; wholly synthetic antibodies; and single chain antibodies. A nonhuman antibody may be humanized by recombinant methods to reduce its immunogenicity in man.

[0048] The antibody may be an antibody that has been altered (e.g., by mutation, deletion, substitution, conjugation to a non-antibody moiety). For example, an antibody may include one or more variant amino acids (compared to a naturally occurring antibody) which change a property (e.g., a functional property) of the antibody. For example, numerous such alterations are known in the art which affect, e.g., half-life, effector function, and/or immune responses to the antibody in a patient. The term antibody also includes artificial polypeptide constructs which comprise at least one antibody-derived antigen binding site.

[0049] The term “antibody-drug conjugate,” as used herein, refers to a compound comprising a monoclonal antibody (mAb) attached to a cytotoxic agent (generally a small molecule drug with a high systemic toxicity) via chemical linkers.

[0050] An “antigen-binding portion” of an antibody (also called an “antigen-binding fragment”) refers to one or more fragments of an antibody that retain the ability to bind specifically to the antigen bound by the whole antibody. It has been shown that the antigen-

binding function of an antibody can be performed by fragments or portions of a full-length antibody. Examples of binding fragments encompassed within the term “antigen-binding portion” or “antigen-binding fragment” of an antibody described herein, include: (1) a Fab fragment (fragment from papain cleavage) or a similar monovalent fragment consisting of the VL, VH, LC and CH1 domains; (2) a F(ab')₂ fragment (fragment from pepsin cleavage) or a similar bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (3) a Fd fragment consisting of the VH and CH1 domains; (4) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; (5) a single domain antibody (dAb) fragment (Ward et al., (1989) *Nature* 341:544-46), which consists of a VH domain; (6) a bi-single domain antibody which consists of two VH domains linked by a hinge (dual-affinity re-targeting antibodies (DARTs)); (7) a dual variable domain immunoglobulin; (8) an isolated complementarity determining region (CDR); and (9) a combination of two or more isolated CDRs, which can optionally be joined by a synthetic linker. Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see, e.g., Bird et al. (1988) *Science* 242:423-426; and Huston et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term “antigen-binding portion” or “antigen-binding fragment” of an antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies. Antigen-binding portions can be produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact immunoglobulins. In some aspects, an antibody is an antigen-binding fragment.

[0051] In some aspects, the antibody-drug conjugate described herein comprises a monoclonal antibody, or an antigen-binding fragment thereof, directed against B-cell Maturation Antigen (BCMA, also known as CD269). BCMA is a member of the tumor necrosis factor receptor superfamily (see, e.g., Thompson et al., *J. Exp. Medicine*, 192(1): 129-135 (2000), and Mackay et al., *Annu. Rev. Immunol.*, 21: 231-264 (2003)). BCMA binds B-cell activating factor (BAFF) and a proliferation inducing ligand (APRIL) (see, e.g., Mackay et al., *supra*, and Kalled

et al., *Immunological Reviews*, 204: 43-54 (2005)). Among nonmalignant cells, BCMA has been reported to be expressed mostly in plasma cells and subsets of mature B-cells (see, e.g., Laabi et al., *EMBO J.*, 77(11): 3897-3904 (1992); Laabi et al., *Nucleic Acids Res.*, 22(7): 1147-1154 (1994); Kalled et al., *supra*; O'Connor et al., *J. Exp. Medicine*, 199(1): 91-97 (2004); and Ng et al., *J. Immunol.*, 173(2): 807-817 (2004)). Mice deficient in BCMA are healthy and have normal numbers of B-cells, but the survival of long-lived plasma cells is impaired (see, e.g., O'Connor et al., *supra*; Xu et al., *Mol. Cell. Biol.*, 21(12): 4067-4074 (2001); and Schiemann et al., *Science*, 293(5537): 2111-2114 (2001)). BCMA RNA has been detected universally in multiple myeloma cells, and BCMA protein has been detected on the surface of plasma cells from multiple myeloma patients by several investigators (see, e.g., Novak et al., *Blood*, 103(2): 689-694 (2004); Neri et al., *Clinical Cancer Research*, 73(19): 5903-5909 (2007); Bellucci et al., *Blood*, 105(10): 3945-3950 (2005); and Moreaux et al., *Blood*, 703(8): 3148- 3157 (2004)).

[0052] The monoclonal antibody, or an antigen-binding fragment thereof, directed against BCMA may comprise any suitable binding affinity to BCMA or an epitope thereof. The term “affinity” refers to the equilibrium constant for the reversible binding of two agents and is expressed as the dissociation constant (K_D). The affinity of an antibody or antigen-binding fragment thereof for an antigen or epitope of interest can be measured using any method known in the art. Such methods include, for example, fluorescence activated cell sorting (FACS), surface plasmon resonance (e.g., BiacoreTM, ProteOnTM), biolayer interferometry (BLI, e.g. Octet), kinetics exclusion assay (e.g. KinExATM), separable beads (e.g., magnetic beads), antigen panning, and/or ELISA (see, e.g., Janeway et al. (eds.), *Immunobiology*, 5th ed., Garland Publishing, New York, N.Y., 2001). It is known in the art that the binding affinity of a particular antibody will vary depending on the method that is used to analyze the binding affinity.

[0053] The term “BCMA-targeted ADC,” as used herein refer to a BCMA-targeted ADC, active in the presence of high levels of soluble BCMA and targets multiple myeloma (MM) progenitor cells.

[0054] The terms “cytotoxin” and “cytotoxic agent” refer to any molecule that inhibits or prevents the function of cells and/or causes destruction of cells (cell death), and/or exerts anti-proliferative effects. It will be appreciated that a cytotoxin or cytotoxic agent of an ADC also is referred to in the art as the “payload” of the ADC.

[0055] The antibody-drug conjugate described herein, or a composition comprising the antibody-drug conjugate, may be contacted with a population of multiple myeloma cells that expresses BCMA *ex vivo*, *in vivo*, or *in vitro*. “*Ex vivo*” refers to methods conducted within or on cells or tissue in an artificial environment outside an organism with minimum alteration of natural conditions. In contrast, the term “*in vivo*” refers to a method that is conducted within living organisms in their normal, intact state, while an “*in vitro*” method is conducted using components of an organism that have been isolated from their usual biological context. In one aspect, the multiple myeloma cells are human multiple myeloma cells that are contacted with the ADC described herein, or a composition comprising the ADC, *in vivo*.

[0056] As used herein, the terms “treatment,” “treating,” and the like refer to obtaining a desired pharmacologic and/or physiologic effect. Preferably, the effect is therapeutic, i.e., the effect partially or completely cures a disease and/or adverse symptom attributable to the disease. To this end, the inventive method comprises administering a “therapeutically effective amount” of the antibody or ADC or the composition comprising the antibody or ADC and a pharmaceutically acceptable carrier. A “therapeutically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result. The therapeutically effective amount may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or ADC to elicit a desired response in the individual. For example, a therapeutically effective amount of the ADC of the invention is an amount which binds to BCMA on multiple myeloma cells and destroys them.

[0057] Alternatively, the pharmacologic and/or physiologic effect may be prophylactic, i.e., the effect completely or partially prevents a disease or symptom thereof. In this respect, the inventive method comprises administering a “prophylactically effective amount” of the ADC or a composition comprising the ADC to a mammal that is predisposed to multiple myeloma. A “prophylactically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired prophylactic result (e.g., prevention of disease onset).

[0058] The ADC described herein, or a composition comprising the antibody ADC, can be administered to a mammal (e.g., a human) using standard administration techniques, including, for example, intravenous, intraperitoneal, and subcutaneous administration. In some aspects, the ADC or composition containing the same is administered to a mammal by intravenous injection.

[0059] The ADC described herein, or the composition comprising the antibody or ADC, can be administered with one or more additional therapeutic agents, which can be coadministered to the mammal. The term “coadministering,” as used herein, refers to administering one or more additional therapeutic agents and the ADC described herein, or the ADC-containing composition, sufficiently close in time such that the ADC can enhance the effect of one or more additional therapeutic agents, or vice versa. In this regard, the ADC or the composition containing the same may be administered first, and the one or more additional therapeutic agents may be administered second, or vice versa. For example, the antibody or ADC or composition containing the same may be administered in combination with other agents (e.g., as an adjuvant) for the treatment or prevention of multiple myeloma. In this respect, the ADC or ADC-containing composition can be used in combination with at least one other anticancer agent including, for example, any suitable chemotherapeutic agent known in the art, ionization radiation, small molecule anticancer agents, cancer vaccines, biological therapies (e.g., other monoclonal antibodies, cancer-killing viruses, gene therapy, and adoptive T-cell transfer), and/or surgery.

[0060] As used herein, “effective treatment” refers to treatment producing a beneficial effect, e.g., amelioration of at least one symptom of a disease or disorder. A beneficial effect can take the form of an improvement over baseline, i.e., an improvement over a measurement or observation made prior to initiation of therapy according to the method. A beneficial effect can also take the form of a competitive overall response rate (ORR). A beneficial effect can also take the form of a promising clinical activity (ORR) in Relapsed/Refractory MM patients who have relapsed on current therapies.

[0061] The term “effective amount” refers to an amount of an agent that provides the desired biological, therapeutic, and/or prophylactic result. That result can be reduction, amelioration, palliation, lessening, delaying, and/or alleviation of one or more of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An effective amount can be administered in one or more administrations. The effective amount of the drug or composition may: (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent and may stop cancer cell infiltration into peripheral organs; (iv) inhibit (i.e., slow to some extent and may stop tumor metastasis; (v) inhibit tumor growth; (vi)

prevent or delay occurrence and/or recurrence of tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer.

[0062] “Dosing interval,” as used herein, means the amount of time that elapses between multiple doses of a formulation disclosed herein being administered to a subject. Dosing interval can thus be indicated as ranges.

[0063] The term “dosing frequency” as used herein refers to the frequency of administering doses of a formulation disclosed herein in a given time. Dosing frequency can be indicated as the number of doses per a given time, e.g., once a week or once in two weeks, etc.

[0064] The terms “about once a week,” “once about every week,” “once about every two weeks,” or any other similar dosing interval terms as used herein means approximate number, and “about once a week” or “once about every week” can include every seven days $\pm$ two days, i.e., every five days to every nine days. The dosing frequency of “once a week” thus can be every five days, every six days, every seven days, every eight days, or every nine days. “Once about every four weeks” can include every 28 days $\pm$ 3 days, i.e., every 25 days to every 31 days. Similar approximations apply, for example, to once about every three weeks, once about every four weeks, once about every five weeks, once about every six weeks and once about every twelve weeks. In some aspects, a dosing interval of once about every four weeks means that the first dose can be administered any day in the first week, and then the next dose can be administered any day in fourth week. In other aspects, a dosing interval of once about every four weeks means that the first dose is administered on a particular day of the first week (e.g., Monday) and then the next dose is administered on the same day of the fourth week (i.e., Monday), respectively.

[0065] A “cancer” refers a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth results in the formation of malignant tumors that may metastasize to distant parts of the body through the lymphatic system or bloodstream.

[0066] The use of the alternative (e.g., “or”) should be understood to mean either one, both, or any combination thereof of the alternatives. As used herein, the indefinite articles “a” or “an” should be understood to refer to “one or more” of any recited or enumerated component.

[0067] The term “and/or” where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term “and/or” as used in a phrase such as “A and/or B” herein is intended to include “A and B,” “A or B,” “A” (alone), and “B” (alone). Likewise, the term “and/or” as used in a phrase such as “A, B, and/or C” is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0068] It is understood that wherever aspects are described herein with the language “comprising,” otherwise analogous aspects described in terms of “consisting of” and/or “consisting essentially of” are also provided.

[0069] The terms “about” or “comprising essentially of” refer to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, i.e., the limitations of the measurement system. For example, “about” or “comprising essentially of” can mean within 1 or more than 1 standard deviation per the practice in the art. Alternatively, “about” or “comprising essentially of” can mean a range of up to 10% or 20% (i.e., $\pm 10\%$ or $\pm 20\%$). For example, about 3 mg can include any number between 2.7 mg and 3.3 mg (for 10%) or between 2.4 mg and 3.6 mg (for 20%). Furthermore, particularly with respect to biological systems or processes, the terms can mean up to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the application and claims, unless otherwise stated, the meaning of “about” or “comprising essentially of” should be assumed to be within an acceptable error range for that particular value or composition.

[0070] As described herein, any concentration range, percentage range, ratio range or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one-tenth and one-hundredth of an integer), unless otherwise indicated.

[0071] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 5th ed., 2013,

Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, 2006, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[0072] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. The headings provided herein are not limitations of the various aspects of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety.

[0073] Various aspects are described in further detail in the following sections.

2. Methods of the Disclosure

[0074] In some aspects, the present disclosure is directed to a method of treating Multiple Myeloma (MM) in a subject in need thereof. In some aspects, the disclosure provides a method of treating Relapsed/Refractory MM in a subject in need thereof. In some aspects, the disclosure provides a method of killing MM cells in a subject in need thereof. In some aspects, the disclosure provides a method of increasing susceptibility MM cells to Natural Killer (NK) cell-mediated killing in a subject in need thereof. In some aspects, the disclosure provides a method of increasing CD38 expression in MM cells in a subject in need thereof. In some aspects, the methods provided herein comprise administering an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) (anti-BCMA ADC) to the subject. A therapy comprising an anti-BCMA ADC results in better therapeutic outcomes (e.g., objective response rate and disease control rate) for afflicted subjects.

[0075] The methods described herein provide the antibody-drug conjugate in an amount that is effective to treat or prevent multiple myeloma. Thus, the disclosure provides a method of killing multiple myeloma cells, which comprises contacting multiple myeloma cells that express BCMA with the antibody-drug conjugate described herein, or a composition comprising the ADC described herein, whereby the antibody-drug conjugate binds to BCMA on the multiple myeloma cells and kills the multiple myeloma cells. The disclosure also provides use of the ADC described herein, or the composition comprising the antibody or ADC, in the manufacture of a medicament for treating multiple myeloma.

[0076] Multiple myeloma, also known as plasma cell myeloma or Kahler's disease, is a cancer of plasma cells, which are a type of white blood cell normally responsible for the production of antibodies (Raab et al., *Lancet*, 374: 324-329 (2009)). Multiple myeloma affects 1-4 per 100,000 people per year. The disease is more common in men, and for yet unknown reasons is twice as common in African Americans as it is in Caucasian Americans. Multiple myeloma is the least common hematological malignancy (14%) and constitutes 1% of all cancers (Raab et al., *supra*). BCMA is highly expressed by multiple myeloma cells (see, e.g., Novak et al., *supra*; Neri et al., *supra*; Bellucci et al., *supra*; and Moreaux et al., *supra*).

[0077] BCMA also is expressed on multiple myeloma stem cells. As such, the disclosure provides a method of killing multiple myeloma stem cells, which comprises contacting multiple myeloma stem cells that express BCMA with the antibody-drug conjugate described herein, or a composition comprising the ADC described herein, whereby the antibody-drug conjugate binds to BCMA on the multiple myeloma stem cells and kills the multiple myeloma stem cells. Multiple myeloma stem cells can be identified in the bone marrow of multiple myeloma patients by their surface expression of CD19 and lack of CD138 surface expression (see, e.g., Matsui et al., *Blood*, 103: 2332-6 (2004)). These cells are uniquely clonogenic and engraft immunodeficient mice, whereas the myeloma plasma cells, defined as CD138+CD19- do not. Multiple myeloma stem cells also are resistant to current therapies (Matsui et al., *Cancer Res.*, 68: 190-7 (2008)).

[0078] In some aspects, the disclosure provides a method of treating Multiple Myeloma (MM) in a subject, the method comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an anti-BCMA ADC. In one aspect, the disclosure provides a method of treating Replapsed/Refractory Multiple Myeloma (MM) in a subject, the method comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an anti-BCMA ADC to the subject. In one aspect, the disclosure provides method of killing Multiple Myeloma (MM) cells in a subject, the method comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an anti-BCMA ADC. In one aspect, the disclosure provides a method of increasing susceptibility Multiple Myeloma (MM) cells to Natural Killer (NK) cell-mediated killing in a subject in need thereof comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an anti-BCMA ADC. In another aspect, the disclosure provides a method

of increasing CD38 expression in Multiple Myeloma (MM) cells in a subject in need thereof comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an anti-BCMA ADC.

[0079] In some aspects of the methods of treating Multiple Myeloma (MM) disclosed herein comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an anti-BCMA ADC. In some aspects, the anti-BCMA ADC comprises an antibody or antigen-binding fragment thereof that specifically binds to BCMA (i.e., an anti-BCMA antibody or antigen-binding fragment thereof).

[0080] In some aspects, the methods treating Multiple Myeloma (MM) in a subject in need thereof disclosed herein comprises administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an anti-BCMA ADC. In some aspects, the method comprises administering about 0.0125 mg/kg, about 0.020 mg/kg, about 0.025 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.10 mg/kg, about 0.11 mg/kg, about 0.12 mg/kg, about 0.13 mg/kg, about 0.14 mg/kg, about 0.15 mg/kg, about 0.16 mg/kg, about 0.17 mg/kg, about 0.18 mg/kg, about 0.19 mg/kg, or about 0.20 mg/kg to the subject. In some aspects, the method of treating Multiple Myeloma (MM) in a subject comprises administering about 0.07 mg/kg of the ADC to the subject. In some aspects, the method of treating Multiple Myeloma (MM) in a subject comprises administering about 0.14 mg/kg of the ADC to the subject. In some aspects, the method of treating Multiple Myeloma (MM) in a subject comprises administering about 0.20 mg/kg of the ADC to the subject.

[0081] In some aspects, the method of treating Multiple Myeloma (MM) in a subject disclosed herein comprises administering a dose of the anti-BCMA ADC to the subject once per treatment cycle. In some aspects, one dose of ADC is administered to the subject once per treatment cycle. In some aspects, a treatment cycle is 28 days. In some aspects, a treatment cycle is about 4 weeks. In some aspects, the ADC is administered once every 3 weeks. In some aspects, the ADC is administered once every 6 weeks.

[0082] In some aspects, the method of treating Multiple Myeloma (MM) in a subject disclosed herein comprises administering the anti-BCMA ADC at a dose of about 0.14 mg/kg once every 3 weeks. In some aspects, the method of treating Multiple Myeloma (MM) in a subject comprises administering the anti-BCMA ADC at a dose of about 0.14 mg/kg once every

6 weeks. In some aspects, the method of treating Multiple Myeloma (MM) in a subject comprises administering the anti-BCMA ADC at a dose of about 0.14 mg/kg once every 3 weeks for two cycles, and then the anti-BCMA ADC is administered at a maintenance dose once every 6 weeks. In some aspects, the maintenance dose is about 0.07 mg/kg.

[0083] In some aspects of the method of treating Multiple Myeloma (MM) disclosed herein, the subject is human.

[0084] In some aspects of the method of treating Multiple Myeloma (MM) in a subject disclosed herein comprises administering a dose of the anti-BCMA ADC to the subject, the administration is intravenous. In some aspects, the administration is intraperitoneal. In some aspects, the administration is subcutaneous.

[0085] In some aspects, the methods of treating Multiple Myeloma (MM) in a subject in need thereof disclosed herein comprises the administration of one or more additional therapeutic agents. In some aspects, the additional therapeutic agents are bortezomib and dexamethasone. In some aspects, the additional therapeutic agent is Daratumumab. In some aspects, the additional therapeutic agents are Lenalidomide and dexamethasone. In some aspects, the anti-BCMA ADC and the one or more additional therapeutic agents are administered simultaneously. In some aspects, the anti-BCMA ADC and the one or more additional therapeutic agents are administered sequentially.

3. ADC Directed Against B-Cell Maturation Antigen (BCMA)

[0086] In some aspects of the present disclosure, the ADC for use in the methods described herein specifically binds to human BCMA and comprises the amino acid sequences of the antibody provided in Table 1.

[0087] The anti-BCMA antibody or antigen-binding fragment thereof of the present disclosure and methods of producing the anti-BCMA antibody or antigen-binding fragment thereof are disclosed in published U.S. Patent Application Pub. No. 2019/0040152 A1, the entirety of which is hereby incorporated by reference.

Table 1. Amino Acid Sequences

	CDR1	CDR2	CDR3
--	------	------	------

VH CDR	SYSMN (SEQ ID NO: 1)	SISGSSNYIYYADSVKG (SEQ ID NO: 2)	GGNYYYVEYFQY (SEQ ID NO: 3)
VL CDR	RASQYISSNYLA (SEQ ID NO: 4)	GASNRAT (SEQ ID NO: 5)	QQYGSSPIT (SEQ ID NO: 6)
VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFRSYSMNWVRQAPGKGLEWVSSISGS SNYIYYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARGGNYYYVEYF QYWGGQGLTVTVSS (SEQ ID NO: 7)		
VL	EIVLTQSPGTLSSLSPGERATLSCRASQYISSNYLAWYQQKPGQAPRLLIYGASNRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPITFGQGKLEIK (SEQ ID NO: 8)		
HC	EVQLVESGGGLVKPGGSLRLSCAASGFTFRSYSMNWVRQAPGKGLEWVSSISGS SNYIYYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARGGNYYYVEYF QYWGGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPPELLGGPSCVFLFPPKPKDTLMISRTPEVTCVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTPPVLDSDGSFFL YSKLTVDKSR WQQGNVFCSS VMHEALHNHY TQKSLSLSPGK (SEQ ID NO: 9)		
LC	EIVLTQSPGTLSSLSPGERATLSCRASQYISSNYLAWYQQKPGQAPRLLIYGASNRA TGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPITFGQGKLEIKRTVAA PSVFIFP PSDEQLKSGT ASVVCLLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSSTL TLISKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 10)		

[0088] In some aspects, the ADC described herein comprises the monoclonal antibody, or an antigen-binding fragment thereof, directed against BCMA. In some aspects, the anti-BCMA antibody or antigen-binding fragment thereof comprises (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6.

[0089] In some aspects, the anti-BCMA antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 7 and/or a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 8.

[0090] In some aspects, the anti-BCMA antibody or antigen-binding fragment thereof comprises a full-length heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 9 and/or a full-length light chain (LC) comprising the amino acid sequence of SEQ ID NO: 10.

[0091] In some aspects, the anti-BCMA antibody or antigen-binding fragment thereof comprises a full-length antibody.

[0092] In some aspects, the anti-BCMA antibody or antigen-binding fragment thereof comprises an antigen binding fragment. In some aspects, the antigen binding fragment comprises a single chain Fv (scFv).

A. Affinity of the anti-BCMA antibody or antigen-binding fragment

[0093] In some aspects of the methods of treating Multiple Myeloma (MM) in a subject disclosed herein, the antibody, or antigen-binding fragment thereof, directed against BCMA may comprise any suitable binding affinity to BCMA or an epitope thereof. The term “affinity” refers to the equilibrium constant for the reversible binding of two agents and is expressed as the dissociation constant (KD). The affinity of an antibody or antigen-binding fragment thereof for an antigen or epitope of interest can be measured using any method known in the art. Such methods include, for example, fluorescence activated cell sorting (FACS), surface plasmon resonance (e.g., Biacore™, ProteOn™), biolayer interferometry (BLI, e.g. Octet), kinetics exclusion assay (e.g. KinExA™), separable beads (e.g., magnetic beads), antigen panning, and/or ELISA (see, e.g., Janeway et al. (eds.), Immunobiology, 5th ed., Garland Publishing, New York, N.Y., 2001). It is known in the art that the binding affinity of a particular antibody will vary depending on the method that is used to analyze the binding affinity.

[0094] A soluble form of BCMA (sBCMA) has been detected in the serum of multiple myeloma patients, with reported values ranging from 3.8 to 1062 ng/mL (Lee et al Br J Haematol 2016, Sanchez et al Br J Haematol 2012), and is comprised of the entire extracellular domain of the molecule (Laurent et. al. Nat Commun 2015). Therefore, sBCMA could diminish the effects of antibody-based therapies. The functional features of sBCMA and recombinant monomeric human BCMA are similar (Laurent et. al. Nat Commun 2015). Therefore, to mitigate the potential effects of sBCMA on the efficacy of a BCMA antibody-drug conjugate, it is desirable to select an antibody component that possesses weak binding to recombinant monomeric human BCMA and strong binding to membrane-bound BCMA.

[0095] Affinity of a binding agent to a ligand, such as affinity of an antibody for an epitope, can be, for example, from about 1 picomolar (pM) to about 1 micromolar (μ M) (e.g., from about 1 picomolar (pM) to about 1 nanomolar (nM), or from about 1 nM to about 1 micromolar (μ M)). In some aspects, the monoclonal antibody or an antigen-binding fragment thereof may bind to BCMA with a K_D less than or equal to 100 nanomolar (e.g., 100 nM, about 90 nM, about 80 nM, about 70 nM, about 60 nM, about 50 nM, about 40 nM, about 30 nM, about 20 nM, or about 10 nM, or a range defined by any two of the foregoing values). In another embodiment, the monoclonal antibody may bind to BCMA with a K_D less than or equal to 10 nanomolar (e.g., about 9 nM, about 8.5 nM, about 8 nM, about 7.5 nM, about 7 nM, about 6.5 nM, about 6 nM, about 5.5 nM, about 5 nM, about 4.5 nM, about 4 nM, about 3.5 nM, about 3 nM, about 2.5 nM, about 2 nM, about 1.5 nM, about 1 nM, about 0.9 nM, about 0.8 nM, about 0.7 nM, about 0.6 nM, about 0.5 nM, about 0.4 nM, about 0.3 nM, about 0.2 nM, about 0.1 nM, about 0.05 nM, about 0.025 nM, about 0.01 nM, about 0.001 nM, or a range defined by any two of the foregoing values). In another embodiment, the monoclonal antibody may bind to BCMA with a K_D less than or equal to 200 pM (e.g., about 190 pM, about 175 pM, about 150 pM, about 125 pM, about 110 pM, about 100 pM, about 90 pM, about 80 pM, about 75 pM, about 60 pM, about 50 pM, about 40 pM, about 30 pM, about 25 pM, about 20 pM, about 15 pM, about 10 pM, about 5 pM, about 1 pM, or a range defined by any two of the foregoing values).

[0096] In some aspects, the affinity of the anti-BCMA antibody or antigen-binding fragment thereof to monomeric (soluble) BCMA, as measured by surface plasmon resonance (SPR), is about 90 nM, about 80 nM, about 70 nM, about 60 nM, about 50 nM, about 40 nM, about 30 nM, or a range defined by any two of the foregoing values, for example, about 50 nM to about 70 nM, about 55 nM to about 65 nM, or about 58 nM to about 62 nM.

[0097] In some aspects of the methods of treating Multiple Myeloma (MM) in a subject disclosed herein, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds strongly to membrane-bound BCMA.

[0098] In some aspects, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds to monomeric (soluble) BCMA with a binding affinity of about 60 nM, as measured by SPR. In some aspects, the anti-BCMA antibody or antigen-binding

fragment thereof binds to monomeric (soluble) BCMA with a binding affinity of 60.7 nM, as measured by SPR.

[0099] In some aspects of the methods of treating Multiple Myeloma (MM) in a subject disclosed herein, the affinity of the anti-BCMA antibody or antigen-binding fragment thereof to membrane-bound BCMA, as measured by flow cytometry (FACS), is less than or equal to 10 nanomolar (e.g., about 9 nM, about 8.5 nM, about 8 nM, about 7.5 nM, about 7 nM, about 6.5 nM, about 6 nM, about 5.5 nM, about 5 nM, about 4.5 nM, about 4 nM, about 3.5 nM, about 3 nM, about 2.5 nM, about 2 nM, about 1.5 nM, about 1 nM, about 0.9 nM, about 0.8 nM, about 0.7 nM, about 0.6 nM, about 0.5 nM, about 0.4 nM, about 0.3 nM, about 0.2 nM, about 0.1 nM, about 0.05 nM, about 0.025 nM, about 0.01 nM, about 0.001 nM, or a range defined by any two of the foregoing values).

[0100] In some aspects of the methods of treating Multiple Myeloma (MM) in a subject disclosed herein, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds weakly to monomeric (soluble) BCMA.

[0101] In some aspects of the methods of treating Multiple Myeloma (MM) in a subject disclosed herein, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds to cell-bound BCMA with a binding affinity of between about 2 nM and 4 nM, as measured by FACS. In some aspects, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds to cell-bound BCMA with a binding affinity of about 3 nM, as measured by FACS.

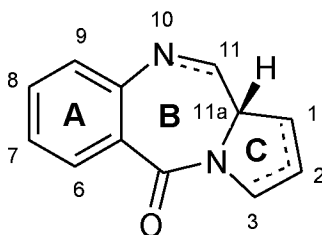
[0102] In some aspects of the methods of treating Multiple Myeloma (MM) in a subject disclosed herein an antigen-binding portion or fragment of an anti-BCMA antibody or antigen-binding fragment thereof can be of any size so long as the portion binds to BCMA. In this respect, an antigen binding portion or fragment of the monoclonal antibody directed against BCMA can comprise between about 5 and 18 amino acids (e.g., about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or a range defined by any two of the foregoing values).

B. Cytotoxic Agents

[0103] The terms “cytotoxin” and “cytotoxic agent” refer to any molecule that inhibits or prevents the function of cells and/or causes destruction of cells (cell death), and/or exerts anti-

proliferative effects. A cytotoxin or cytotoxic agent of an ADC also is referred to in the art as the “payload” of the ADC. A number of classes of cytotoxic agents are known in the art to have potential utility in ADC molecules and can be used in the ADC described herein. Such classes of cytotoxic agents include, for example, anti-microtubule agents (e.g., auristatins and maytansinoids), pyrrolobenzodiazepines (PBDs), RNA polymerase II inhibitors (e.g., amatoxins), and DNA alkylating agents (e.g., indolinobenzodiazepine pseudodimers). Examples of specific cytotoxic agents that may be used in the ADC described herein include, but are not limited to, amanitins, auristatins, calicheamicin, daunomycins, doxorubicins, duocarmycins, dolastatins, enediynes, lexitropsins, taxanes, puromycins, maytansinoids, vinca alkaloids, tubulysins, and pyrrolobenzodiazepines (PBDs). More specifically, the cytotoxic agent may be, for example AFP, MMAF, MMAE, AEB, AEVB, auristatin E, paclitaxel, docetaxel, CC-1065, SN-38, topotecan, morpholino-doxorubicin, rhizoxin, cyanomorpholino-doxorubicin, dolastatin-10, echinomycin, combretastatin, chaliceamicin, maytansine, DM1, DM4, vinblastine, methotrexate, netropsin, or derivatives or analogs thereof. Cytotoxins suitable for use in ADCs are also described in, for example, International Patent Application Publication Nos. WO 2015/155345 and WO 2015/157592.

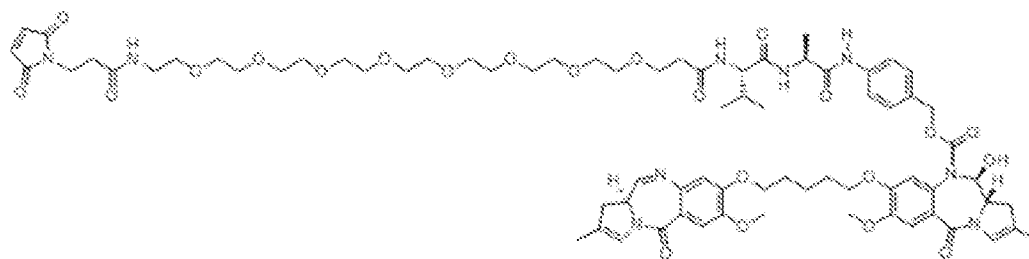
[0104] In some aspects, the cytotoxic agent may be a pyrrolobenzodiazepine (PBD) or a PBD derivative. PBD translocates to the nucleus where it crosslinks DNA, preventing replication during mitosis, damaging DNA by inducing single strand breaks, and subsequently leading to apoptosis. Some PBDs also have the ability to recognize and bind to specific sequences of DNA. PBDs are of the general structure:



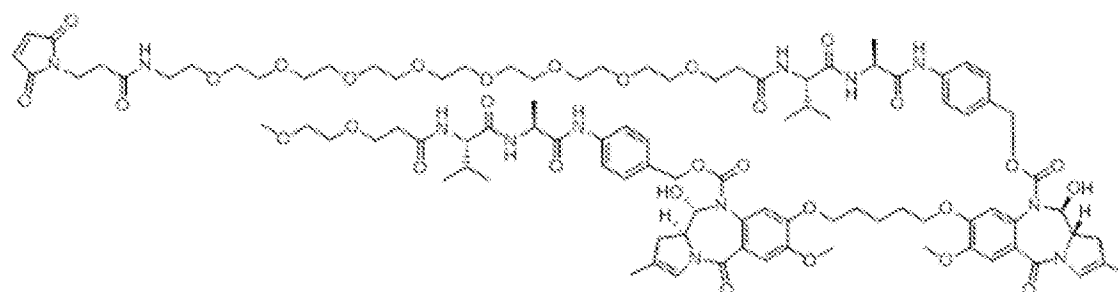
[0105] PBDs differ in the number, type, and position of substituents, in both their aromatic A rings and pyrrolo C rings, and in the degree of saturation of the C ring. In the B-ring there is either an imine (N=C), a carbinolamine (NH-CH(OH)), or a carbinolamine methyl ether (NH-CH(OMe)) at the N10-C11 position, which is the electrophilic centre responsible for alkylating

DNA. All of the known natural products have an (S)-configuration at the chiral C11a position which provides them with a right-handed twist when viewed from the C ring towards the A ring. This feature also gives PBDs the appropriate three-dimensional shape for isohelicity with the minor groove of B-form DNA, leading to a snug fit at the binding site (Kohn, In: *Antibiotics III*. Springer-Verlag, New York, pp. 3-11 (1975); and Hurley and Needham-VanDevanter, *Acc. Chem. Res.*, 19: 230-237 (1986)). PBDs can form adducts in the minor groove, leading to interference with DNA processing.

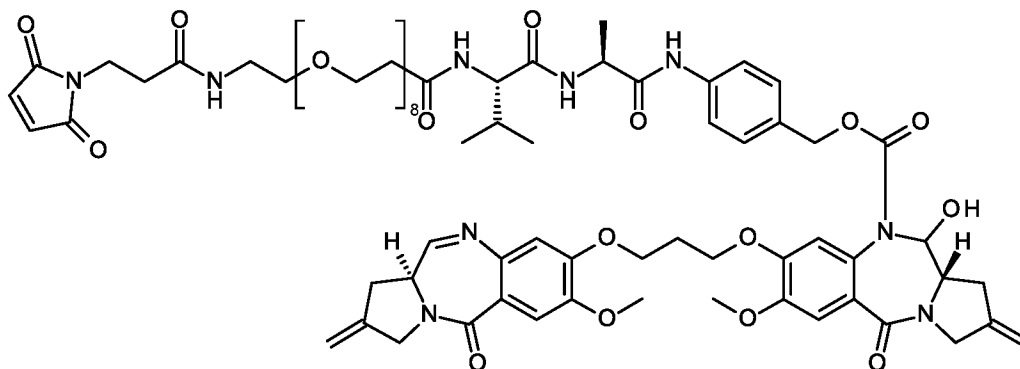
[0106] In one aspect, the PBD is PBD 3249, also referred to herein as “SG3249” and described in detail in WO 2014/057074, which has the following structure:



[0107] In one aspect, the PBD is PBD 3315, also referred to herein as “SG3315” and described in detail in WO 2015/052322, which has the following structure:



[0108] In another aspect, the PBD is SG3400, also referred to as Compound 23, which is described in detail in PCT/EP2017/052988, filed on 10 February 2017, and has the following structure:



C. Linker

[0109] In some aspects of the methods of treating Multiple Myeloma (MM) in a subject disclosed herein, the anti-BCMA antibody, or antigen-binding fragment thereof, may be conjugated to a cytotoxin using any suitable method known in the art, including site-specific or non-site specific conjugation methods. Conventional conjugation strategies for antibodies typically rely on randomly (i.e., non-specifically) conjugating the payload to the antibody or antigen-binding fragment thereof, through lysines or cysteines.

[0110] In some aspects, the cytotoxic agent may be conjugated to the BCMA monoclonal antibody using site-specific conjugation methods at specific reactive amino acid residues, yielding homogeneous ADC preparations with uniform stoichiometry. Site-specific conjugation may be through a cysteine residue or a non-natural amino acid. In one embodiment, the cytotoxic agent may be conjugated to the antibody, or antigen binding fragment thereof, through at least one cysteine residue. In particular, for example, a cytotoxic agent may be chemically conjugated to the side chain of an amino acid at a specific Kabat position in the Fc region of the anti-BCMA antibody. In this regard, the cytotoxic agent may be conjugated to the anti-BCMA antibody through a cysteine residue at any suitable position in the Fc region of the antibody, including but not limited to, a cysteine at least one of positions 239, 248, 254, 273, 279, 282, 284, 286, 287, 289, 297, 298, 312, 324, 326, 330, 335, 337, 339, 350, 355, 356, 359, 360, 361, 375, 383, 384, 389, 398, 400, 413, 415, 418, 422, 440, 441, 442, 443 and 446, wherein the numbering corresponds to the EU index in Kabat. In one embodiment, the cytotoxic agent may be conjugated to the anti-BCMA antibody through a cysteine residue at the specific Kabat positions

239 and/or 442 of the BCMA monoclonal antibody, and/or through an amino acid residue inserted between Kabat positions 239 and 240 of the BCMA antibody (Dimasi et al., *Mol Pharm*, 14(5):1501-1516 (2017). Alternatively, the cytotoxic agent may be conjugated to the anti-BCMA antibody or antigen binding fragment thereof through a thiol-maleimide linkage, such as, for example, via a sulfhydryl reactive group at the hinge and heavy-light chains.

[0111] The anti-BCMA antibody described herein comprises at least one cytotoxin molecule conjugated thereto; however, the anti-BCMA antibody may comprise any suitable number of cytotoxin molecules conjugated thereto (e.g., 1, 2, 3, 4, or more cytotoxin molecules) to achieve a desired therapeutic effect. In one aspect, the ADC described herein comprises two cytotoxin molecules conjugated to a BCMA monoclonal antibody.

[0112] In some aspects of the methods of treating Multiple Myeloma (MM) in a subject in need thereof disclosed herein, the ADC is site-specifically conjugated to a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer via a protease-cleavable linker. Without wishing to be bound to any particular theory or mechanism, it is thought that after cell surface binding to BCMA, the ADC is internalized and cleaved in the lysosomal compartment, releasing the active PBD, which cross-links DNA and leads to apoptotic cell death.

[0113] In some aspects of the methods of treating Multiple Myeloma (MM) in a subject in need thereof disclosed herein, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof conjugated to a cytotoxin via a linker. In some aspects, the linker is a protease-cleavable linker. In some aspects, the cytotoxin is a pyrrolobenzodiazepine (PBD). In some aspects, the PBD is a DNA cross-linking PBD dimer.

[0114] In some aspects of the methods of treating Multiple Myeloma (MM) in a subject in need thereof disclosed herein, the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof, wherein the Fc effector function of the anti-BCMA antibody or antigen-binding fragment thereof is eliminated.

[0115] In some aspects, the method of treating Multiple Myeloma (MM) in a subject disclosed herein comprises intravenously administering 0.14 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) every 3 weeks, wherein the ADC comprises: (a) an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1)

amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6; (b) a protease-cleavable linker; and (c) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer.

[0116] In some aspects, the method of treating Multiple Myeloma (MM) in a subject disclosed herein comprises intravenously administering 0.14 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) every 6 weeks, wherein the ADC comprises: (a) an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6; (b) a protease-cleavable linker; and (c) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer.

[0117] In some aspects, the method of treating Multiple Myeloma (MM) in a subject disclosed herein comprises intravenously administering 0.14 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) every 3 weeks for 2 cycles, and then intravenously administering 0.07 mg/kg of the ADC every 6 weeks, wherein the ADC comprises: (a) an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6; (b) a protease-cleavable linker; and (c) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer.

[0118] In some aspects, the method of treating Multiple Myeloma (MM) in a subject disclosed herein comprises intravenously administering 0.10 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) every 3 weeks for at least 6 months, wherein the ADC comprises: (a) an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6; (b) a protease-cleavable linker; and (c) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer.

[0119] In some aspects, the method of treating Multiple Myeloma (MM) in a subject disclosed herein results in a response in the subject for a duration of at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, or at least 12 months. In some aspects, the method of treating Multiple Myeloma (MM) in a subject disclosed herein results in a response in the subject for a duration of at least one year.

4. Patient Populations and Outcomes

[0120] Provided herein are clinical methods for treating cancers (e.g., Multiple Myeloma (MM), and relapsed/refractory MM) in human patients using any method disclosed herein, for example, an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) (anti-BCMA ADC) administered as a single agent or optionally in combination with one or more chemotherapeutic agents.

[0121] Therapeutic or prophylactic efficacy can be monitored by periodic assessment of treated patients. In some aspects, the ADC described herein inhibits or suppresses proliferation of BCMA-expressing myeloma cells by at least about 10% (e.g., at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 100%). Cell proliferation can be measured using any suitable method known in the art, such as measuring incorporation of labeled

nucleosides (e.g., 3H-thymidine or bromodeoxyuridine Brd(U)) into genomic DNA (see, e.g., Madhavan, H.N., J. Stem Cells Regen. Med., 3(1): 12-14 (2007)).

[0122] A known drawback of available MM treatment is eye toxicity. Advantageously, administration of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) described herein does not result in significant epithelial changes in the cornea.

5. Pharmaceutical Compositions

[0123] Pharmaceutical compositions suitable for administration to human patients are typically formulated for parenteral administration, e.g., in a liquid carrier, or suitable for reconstitution into liquid solution or suspension for intravenous administration.

[0124] In general, such compositions typically comprise a pharmaceutically acceptable carrier. As used herein, the term “pharmaceutically acceptable” means approved by a government regulatory agency or listed in the U.S. Pharmacopeia or another generally recognized pharmacopeia for use in animals, particularly in humans. The term “carrier” refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil, glycerol polyethylene glycol ricinoleate, and the like. Water or aqueous solution saline and aqueous dextrose and glycerol solutions may be employed as carriers, particularly for injectable solutions. Liquid compositions for parenteral administration can be formulated for administration by injection or continuous infusion. Routes of administration by injection or infusion include intravenous, intraperitoneal, intramuscular, intrathecal and subcutaneous.

EXAMPLES

Example 1: Phase 1, First-in-Human Study of a BCMA-Targeted ADC in Patients With Relapsed/Refractory Multiple Myeloma

[0125] In this Phase 1, First-in-Human, open-label study, eligible patients were ≥ 18 years old with confirmed R/R MM as defined by International Myeloma Working Group consensus criteria, had measurable disease, and had an Eastern Cooperative Oncology Group performance

status ≤ 1 . This study is to evaluate the safety, PK, immunogenicity, pharmacodynamics (PD), and preliminary efficacy of single agent BCMA-Targeted ADC in adult subjects with multiple myeloma (MM) who are considered to be relapsed, or refractory to standard anti-myeloma therapies, and in addition, are either ineligible for standard salvage regimens or for whom there are no standard salvage regimens available(hereafter referred to as R/R MM). Patients progressed after treatment with three classes of standard-of-care antimyeloma drugs, including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies (mAbs). The study consists a dose-escalation phase and dose-expansion phase. Dose escalation was based on an accelerated titration design, with an mTPI-2 algorithm.

Primary objective:

[0126] In this study, the safety and tolerability of the BCMA-Targeted ADC was assessed, dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), maximum administered dose (MAD), and recommended dose (RD) were defined.

Secondary objectives:

- To evaluate the preliminary efficacy of anti-BCMA ADC monotherapy
- To describe the pharmacokinetics (PK)
- To determine the immunogenicity

Exploratory objectives:

- To evaluate the potential relationship between baseline BCMA expression (evaluated in fresh bone marrow biopsy and aspirate [BM] samples collected at study entry) and clinical response to anti-BCMA ADC in subjects with R/R MM
- To explore the relationship between genomic alterations and clinical response to the anti-BCMA ADC in subjects with R/R MM
- To evaluate the potential relationship between baseline genomic mutations and transcriptional deregulation in the DNA damage response (DDR) pathway and clinical response to anti-BCMA ADC in subjects with R/R MM
- To examine the effects on pharmacodynamic biomarkers (eg, induction of γ H2AX expression and other mechanism-related biomarkers) in subjects with R/R MM

STUDY ENDPOINTS

Primary endpoints:

- Safety and tolerability as assessed by the incidence rates of adverse events (AEs), serious adverse events (SAEs), DLTs as well as frequency of changes from baseline in laboratory toxicity grade parameters, vital signs, and electrocardiogram (ECG) results

Secondary endpoints:

- Objective response rate (ORR), clinical benefit rate (CBR), duration of response (DoR), progression-free survival (PFS), and overall survival (OS)
- The endpoints for assessment of PK include individual subject concentrations (including active anti-BCMA ADC, total antibody, and free warhead) in plasma at different time points after administration.
- Pharmacokinetic parameters include, but are not limited to, maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), clearance (CL), and terminal half-life (t_{1/2}).
- The endpoints for assessment of immunogenicity include the number and percentage of subjects who develop treatment-emergent anti-drug antibodies (ADAs).

Exploratory endpoints:

- The endpoints for assessment of exploratory biomarkers are listed in the table below. These endpoints are assessed at baseline and at selected time points after administration of anti-BCMA ADC.
- Minimal residual disease (MRD) is assessed as an exploratory tumor disease endpoint after confirmed complete response(s) are achieved.

Biomarkers	Predictive	Pharmacodynamics
Baseline BCMA protein levels in pre-treatment BM	X	
Baseline DDR mutation and genomic profiles in pre-treatment BM	X	
Baseline and on-treatment serum/whole blood biomarkers	X	X
Baseline and on-treatment mechanism-related biomarkers in BM, if available		X
Baseline and on-treatment ctDNA in plasma	X	X

BCMA = B-cell maturation antigen; BM = bone marrow; ctDNA = circulating tumor DNA; DDR = DNA damage response.

Note: BM refers to bone marrow biopsies and/or bone marrow aspirates. Baseline refers to fresh BM samples collected at study entry.

- [0127] The sequentially ascending dose levels start from a starting dose of 0.025 mg/kg administered via intravenous infusion on Day 1 of each 3-week cycle (Q3W). The 8 main dose levels are 0.025 mg/kg, 0.05 mg/kg, 0.10 mg/kg, 0.20 mg/kg, 0.31 mg/kg, 0.51 mg/kg, 0.80 mg/kg, and 1.25 mg/kg. Intermediate dose levels of 0.035 mg/kg, 0.07 mg/kg, 0.14 mg/kg, 0.24 mg/kg, 0.37 mg/kg, 0.55 mg/kg, and 0.82 mg/kg were de-escalation doses. /kg and 1.5 mg/kg; 25% and 20% escalation increments respectively) may be evaluated.
- [0128] Administration of the first dose in each dose-escalation cohort is staggered by a minimum of 48 hours between the first and second subjects. Treatment continues until disease progression, unacceptable toxicity, or withdrawal of consent.

INCLUSION CRITERIA

- [0129] Subjects must be ≥ 18 years of age at the time of screening.
- [0130] Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the USA, European Union [EU] Data Privacy Directive in the EU) must be obtained from the patient prior to performing any protocol-related procedures, including screening evaluations.
- [0131] Subjects must have a confirmed diagnosis of multiple myeloma with measurable disease per IMWG criteria (Kumar et al, 2016) requiring systemic therapy.
- [0132] Subjects must be considered to be relapsed or refractory to standard anti-myeloma therapies as defined by IMWG consensus recommendations (Rajkumar et al, 2011):
- [0133] Relapsed myeloma: previously treated myeloma that progresses and requires the initiation of salvage therapy but does not meet criteria for either “primary refractory myeloma” or “relapsed-and-refractory myeloma” categories.
- [0134] Refractory myeloma: disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either

failure to achieve minimal response or development of progressive disease (PD) while on therapy.

[0135] Subjects must either be ineligible for, or have no standard salvage treatment options available.

[0136] For the dose-escalation phase: Subjects must have failed prior standard anti-myeloma therapy.

[0137] For the dose-expansion phase: Subjects must have had ≥ 2 lines of therapy with all of the 3 following classes of anti-myeloma drugs: proteasome inhibitors, immunomodulatory drugs (IMiDs) and monoclonal antibodies.

[0138] Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.

[0139] Adequate organ and marrow functions as determined by:

- Absolute neutrophil count $\geq 1.0 \times 10^9 /L$ (≥ 7 days following last dose of GCSF therapy)
- Platelet count $\geq 50 \times 10^9 /L$ (≥ 7 days following platelet transfusion)
- Hemoglobin ≥ 8.0 g/dL (≥ 14 days following PRBC transfusion)
- Calculated creatinine clearance ≥ 40 mL/min or serum creatinine $\leq 1.5 \times$ ULN
- Total bilirubin $\leq 1.5 \times$ ULN (unless consistent with Gilbert's syndrome [ratio between total and direct bilirubin > 5], for which TBL $\leq 3.0 \times$ ULN is allowed)
- AST and ALT $\leq 3 \times$ ULN

[0140] Baseline fresh bone marrow biopsy and aspirate samples are mandatory for each subject prior to study entry.

[0141] Prior to being dosed with study drug on Cycle 1 Day 1:

[0142] All prior treatment-related non-hematological toxicities must be National Cancer Institute - Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.03 $\leq$ Grade 1 at the time of enrollment (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 RT
- At least 14 days must have elapsed following 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 treatment with Mab treatment of MM

- At least 21 days must have elapsed or complete healing of incision must have occurred (whichever occurs sooner) after major surgery
- At least 14 days or five half-lives of any investigational drug (whichever is shorter) must have elapsed

RESULTS

[0143] During dose escalation, the anti-BCMA ADC was administered in sequentially ascending dose levels (0.0125, 0.025, 0.05, 0.1, and 0.2 mg/kg) intravenously every 3 weeks (Q3W) (**FIG. 1**). Due to dose-limiting toxicities (DLTs), the 0.2 mg/kg dose was de-escalated to an intermediate dose level of 0.14 mg/kg.

[0144] All patients had received prior therapy with an IMiD, PI, and mAb: lenalidomide, 76 (94%); pomalidomide, 68 (84%); bortezomib, 77 (95%); carfilzomib, 64 (79%); and daratumumab, 71 (87%). Twenty patients received ≥ 5 lines of prior therapy. At 0.2 mg/kg, 2 patients experienced dose-limiting toxicities (DLTs) (grade 3/4 thrombocytopenia) without bleeding; no DLTs were reported for other dose levels.

[0145] Efficacy was demonstrated at all dose levels in the dose escalation phase (**FIG. 2**), shown below in dose mg/kg, objective response rate [ORR], and [n]).

Dose Escalation Phase Cohorts

- Cohort 1: 0.0125 mg/kg, 33.3% [1/3];
- Cohort 2: 0.025 mg/kg, 16.7% [1/6];
- Cohort 3: 0.05 mg/kg, 33.3% [3/9];
- Cohort 4: 0.10 mg/kg, 27.8% [5/18];
- Cohort 4A: 0.14 mg/kg, 61.0% [25/41]; and
- Cohort 5: 0.2 mg/kg, 40.0%, [2/5]

[0146] The maximum tolerated dose was 0.14 mg/kg administered every three weeks. This dose was used as a basis for expansion Cohorts A, B, and C.

MTD Expansion Phase Cohorts

- Cohort A: 0.14 mg/kg Q3W
- Cohort B: 0.14 mg/kg Q6W

[0147] The anti-BCMA ADC exhibited linear PK at doses of ≥ 0.05 mg/kg Q3W (**FIG. 3**). The mean terminal half-life is 6 to 9 days. BCMA expression was assessed on marrow biopsies by immunohistochemistry (IHC)

- 66 patients assessed (Hematogenix)
- 22 patients with insufficient viable sample were not included in analysis
- *9 Patients not represented due to screen fail, rapid progression or SAE

[0148] The IHC readouts indicated (1) the % CD138+ that are BCMA+ and (2) the % of tumor cells that are 1+ and 2+ intensity.

[0149] A BCMA modified H-score was calculated based on % BCMA and intensity.

- Formula: $(1 \times (\%1+) + 2 \times (\%2+)) \times (\%BCMA+CD138+/100)$

[0150] There was no difference in BCMA expression by IHC in the bone marrow of responders compared with nonresponders. The majority of patients had $\geq 80\%$ CD138+ plasma cells that are BCMA+ in the screening bone marrow (BM) biopsy.

[0151] IHC expression also confirmed that levels of BCMA are similar in patients pre-treated with daratumumab compared to those not previously treated with daratumumab (but may have been treated with other agents).

[0152] In the 0.14 mg/kg cohort, the overall response rate (ORR) was high, at 61.0% (95% confidence interval [CI]: 44.5%, 75.8%). There were 10 (24.4%) very good partial responses (VGPRs), 15 (36.6%) partial responses, and 3 (7.3%) minimal responses (**FIG. 4** and **Table 2**). Four of the VGPR patients were immunofixation negative. Most (90.2%) patients in the 0.14 mg/kg cohort had received prior daratumumab. The median duration of response (DoR) in the 0.14 mg/kg cohort was not reached. The median DoR for all patients was 8.7 months.

[0153] Treatment-related adverse events (TEAEs) that occurred in $\geq 20\%$ of patients in the 0.14 mg/kg cohort in the dose expansion phase were photophobia (53.7%), thrombocytopenia (31.7%), rash (29.3%), increased gamma-glutamyltransferase (24.4%), dry eye (20.0%), and pleural effusion (20.0%). Keratopathy or visual acuity loss were not observed in this cohort. The TEAE profiles at lower-dose levels were similar but with lower incidences compared with the 0.14 mg/kg level.

Table 2. Efficacy (Best Overall Response) at the 0.14 mg/kg Dose Level

	0.14 mg/kg N=41
ORR	25 (61.0%) 95% CI: 44.5%, 75.8%
CR/sCR	0
VGPR	10 (24.4%)
PR	15 (36.6%)
MR	3 (7.3%)
SD	6 (14.6%)
PD	5 (12.2%)
NE	1 (2.4%)
Median time to response	2.1 mo (95% CI: 0.7, 2.8)

ORR = overall response rate; CR= complete response; VGPR = very good partial response; PR = partial response; MR = minimal response; SD = stable disease; PD = progressive disease
NE = not evaluable

[0154] Thirty-six patients in the 0.14 mg/kg cohort (Cohort A) discontinued treatment due to adverse events (n=24), progressive disease (n=8), patient decision (n=2), investigator decision (n=1), and death (n=1). However, in this cohort, the patients showed signal of response durability (**FIG. 5**). As shown, there were early and late responses to the anti-BCMA ADC even with missed cycles in this cohort.

[0155] Treatment related adverse events by grade and frequency in Cohort A are provided below in Table 3.

Table 3.

Preferred Term	All (N=41)	Grade 1-2	Grade 3-4
Subjects with at least one related event	39 (95.1%)	33 (80.5%)	27 (65.9%)
Photophobia	22 (53.7%)	16 (39.0%)	6 (14.6%)*
Rash / maculopapular rash	15 (36.6%)	15 (36.6%)	0
Thrombocytopenia	15 (36.6%)	4 (9.8%)	11 (26.8%)

Oedema peripheral /oedema	10 (24.4%)	9 (22.0%)	1 (2.4%)
GGT Increase	10 (24.4%)	2 (4.9%)	8 (19.5%)
Pleural effusion	8 (19.5%)	7 (17.1%)	1 (2.4%)
Dry Eye	8 (19.5%)	5 (12.2%)	3 (7.3%)*
Neutropenia	7 (17.1%)	1 (2.4%)	6 (14.6%)
Anaemia	6 (14.6%)	4 (9.8%)	2 (4.9%)
Blood Alk phos increase	6 (14.6%)	2 (4.9%)	4 (9.8%)
Decreased appetite	6 (14.6%)	6 (14.6%)	0
Periorbital oedema/ swelling	6 (14.6%)	6 (14.6%)	0
Photosensitivity reaction	6 (14.6%)	5 (12.2%)	1 (2.4%)
Vision Blurred	6 (14.6%)	6 (14.6%)	0
ALT increase	5 (12.2%)	5 (12.2%)	0
AST increase	5 (12.2%)	5 (12.2%)	0
Eye pain	5 (12.2%)	5 (12.2%)	0
Lacrimation increased	5 (12.2%)	5 (12.2%)	0

[0156] The 0.1 mg/kg dose level (Cohort 4 in the dose escalation phase) showed an encouraging duration of response, as shown in **FIG. 6** and Table 4, below.

Table 4. Duration of Response

Subject	DoR (days/mo)	Status
A	232/7m+	On TRT
B	299/10m	Off TRT
C	330/10m +	Off TRT
D	265/~9m	Off Study (died)
E	52/~2m	Off Study (WC)

[0157] This example demonstrates that the BCMA-targeted ADC demonstrated clinical efficacy at all dose levels explored. Administration at the 0.14 mg/kg dose administered every 3 weeks had a manageable safety profile and an ORR of 61% in a heavily pretreated population

with myeloma that is R/R post PI, IMiD, mAb (90.2% of patients had received prior daratumumab), and other standard-of-care therapies, as shown in Table 5.

Table 5. Disease Response by Number of Prior Regimens in Cohort A

	≥1 and ≤4 Prior Regimen N=22	≥ 5 and ≤ 7 Prior Regimen N=11	≥ 8 and ≤11 Prior Regimen N=8
ORR* (95%CI)	11 (50.0%) (28.2%, 71.8%)	8 (72.7%) (39.0%, 94.0%)	6 (75.0%) (34.9%, 96.8%)

Example 2: Clinical Benefit in High & Low Risk Populations

Administration at the 0.14 mg/kg dose was investigated with regard to cytogenetics. The administration of the anti-BCMA ADC at the 0.14 mg/kg dose showed a comparable clinical benefit in high and low risk cytogenetic populations, as shown in Table 6.

Table 6. Disease Response by Cytogenetics Risk

	0.14 mg/kg Q					
	High Risk				Low Risk	
	IGH1416 N=4	IGH414 N=2	DEL17P N=5	1q21 N=8	Total N=14	Total N=27
CR+PR (objective response)	1 (25.0%)	1 (50.0%)	2 (40.0%)	7 (87.5%)	8 (57.1%)	17 (63.0%)
95% C.I.	(0.6%, 80.6%)	(1.3%, 98.7%)	(5.3%, 85.3%)	(47.3%, 99.7%)	(28.9%, 82.3%)	(42.4%, 80.6%)
80% C.I.	(2.6%, 68.0%)	(5.1%, 94.9%)	(11.2%, 75.3%)	(59.4%, 98.7%)	(36.9%, 75.7%)	(48.8%, 75.6%)

Example 3: Comparison of Treatment Emergent Corneal Events

[0158] Treatment emergent corneal events due to the administration of the anti-BCMA ADC in Cohort A (n=41) was compared to treatment emergent corneal events due to the administration of Belantamab Mafodotin at a dose of 2.5 mg/kg. The results are provided in Tables 7A and 7B, respectively. As shown, ocular toxicity due to the administration of the anti-BCMA ADC is not a class effect and does not result in significant epithelial changes in the cornea.

Table 7A. Treatment Emergent Corneal Events - anti-BCMA ADC

Preferred Term	Number of pts (%)
Any corneal disorder	27 (65.9%)
Photophobia	22 (53.7%)
Dry eye	11 (26.8%)
Blurred vision	7 (17.1%)

Table 7B. Treatment Emergent Corneal Events - Belantamab Mafodotin

Preferred Term	Number of pts (%)
Corneal events	68 (72%)^
Keratopathy (corneal epithelial change)	68 (72%)
Dry eye	14 (15%)
Blurred vision	21 (25%)

[0159] Photophobia (discomfort or pain to the eyes due to light exposure) is a key factor affecting quality of life for patients undergoing treatment for Multiple Myeloma. Eye toxicity is not a known class effect of the DNA cross-linking pyrrolobenzodiazepine (PBD) payload in the anti-BCMA ADC. A key symptom discovered during the Phase 1, first-in-human study described herein related to drug administration is photophobia. However, while patients were symptomatic (i.e., they reported photophobia, eye pain, dry eye, blepharitis, inability to read, drive, look at tv, dark glasses indoors sitting in dark rooms) no significant corneal changes were found upon ophthalmology examinations.

[0160] In contrast, all corneal events associated with the administration of Belantamab Mafodotin at a dose of 2.5 mg/kg resulted in corneal epithelium changes, and a prophylactic steroid regimen had no impact on corneal events. Corneal epithelial changes are a known class effect for the monomethyl auristatin F (MMAF) payload in this conjugate. This protocol requires an ophthalmology exam prior to each dose. Keratopathy accounted for 88% of dose interruptions in this regimen. While 69% of patients re-initiated treatment at the interim analysis, the median time to re-initiation was 83 days (range 28-146), which was about 4 cycles. Additionally, dose

delays due to keratopathy started at week 4 (about 1 cycle), and dose reductions started at week 13 (about 4 cycles).

[0161] This example demonstrates that administration of the anti-BCMA ADC disclosed herein does not cause significant corneal changes, in contrast to the administration of Belantamab Mafodotin.

WHAT IS CLAIMED:

1. A method of treating Multiple Myeloma (MM) in a subject, the method comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an antibody-drug conjugate (ADC), wherein the ADC is directed against B-Cell Maturation Antigen (BCMA).
2. A method of treating Relapsed/Refractory Multiple Myeloma (MM) in a subject, the method comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an antibody-drug conjugate (ADC), wherein the ADC is directed against B-Cell Maturation Antigen (BCMA).
3. A method of killing multiple myeloma (MM) cells in a subject, the method comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an antibody-drug conjugate (ADC), wherein the ADC directed against B-Cell Maturation Antigen (BCMA).
4. A method of increasing susceptibility Multiple Myeloma (MM) cells to Natural Killer (NK) cell-mediated killing in a subject in need thereof comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA).
5. A method of increasing CD38 expression in Multiple Myeloma (MM) cells in a subject in need thereof comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA).
6. The method of any of claims 1-5, wherein the ADC comprises an antibody or antigen-binding fragment thereof that specifically binds to BCMA (anti-BCMA antibody or antigen-binding fragment thereof).

7. The method of any one of claims 1-6, comprising administering to the subject about 0.0125 mg/kg, about 0.025 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.10 mg/kg, about 0.11 mg/kg, about 0.12 mg/kg, about 0.13 mg/kg, about 0.14 mg/kg, about 0.15 mg/kg, about 0.16 mg/kg, about 0.17 mg/kg, about 0.18 mg/kg, about 0.19 mg/kg, or about 0.20 mg/kg,
8. The method of any one of claims 1-7, comprising administering about 0.14 mg/kg of the ADC to the subject.
9. The method of any one of claims 1-7, comprising administering about 0.20 mg/kg of the ADC to the subject.
10. The method of any one of claims 1-9, wherein one dose of ADC is administered to the subject once per treatment cycle.
11. The method of claim 10, wherein a treatment cycle is 28 days.
12. The method of claim 11, wherein a treatment cycle is about 4 weeks.
13. The method of any one of claims 1-12, wherein the ADC is administered once every 3 weeks.
14. The method of any one of claims 1-12, wherein the ADC is administered once every 6 weeks.
15. The method of any one of claims 1-12, wherein the ADC is administered at a dose of about 0.14 mg/kg once every 3 weeks.

16. The method of any one of claims 1-12, wherein the ADC is administered at a dose of about 0.14 mg/kg once every 6 weeks.
17. The method of any one of claims 1-16, wherein the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds strongly to membrane-bound BCMA.
18. The method of any one of claims 1-17, wherein the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds weakly to monomeric (soluble) BCMA.
19. The method of any one of claims 1-18, wherein the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds to monomeric (soluble) BCMA with a binding affinity of about 60 nM, as measured by surface plasmon resonance.
20. The method of claim 19, wherein the anti-BCMA antibody or antigen-binding fragment thereof binds to monomeric (soluble) BCMA with a binding affinity of 60.7 nM, as measured by surface plasmon resonance.
21. The method of any one of claims 1-20, wherein the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds to cell-bound BCMA with a binding affinity of between about 2 nM and 4 nM, as measured by flow cytometry.
22. The method of claim 21, wherein the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that binds to cell-bound BCMA with a binding affinity of about 3 nM, as measured by flow cytometry.
23. The method of any one of claims 1-22, wherein the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof conjugated to a cytotoxin via a linker.
24. The method of claim 22, wherein the linker is a protease-cleavable linker.

25. The method of claim 23 or 24, wherein the cytotoxin is a pyrrolobenzodiazepine (PBD).
26. The method of claim 25, wherein the PBD is a DNA cross-linking PBD dimer.
27. The method of any one of claims 1-26, wherein the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof, wherein the Fc effector function of the anti-BCMA antibody or antigen-binding fragment thereof is eliminated.
28. The method of any one of claims 1-27, wherein the administration does not result in significant epithelial changes in the cornea.
29. The method of any one of claims 1-28, further comprising measuring BCMA expression in plasma cells obtained from the subject.
30. The method of claim 29, wherein the plasma cells are obtained from a bone marrow biopsy from the subject.
31. The method of any one of claims 1-30, wherein BCMA expression is assessed by immunohistochemistry (IHC).
32. The method of claim 30 or 31, wherein the bone marrow biopsy contains $\geq 80\%$ CD138+ plasma cells that are BCMA+.
33. The method of any one of claims 1-32, wherein the antibody-drug conjugate (ADC), directed against B-Cell Maturation Antigen (BCMA) is administered to a cohort of subjects.
34. The method of claim 33, wherein the administration results in an overall response rate of at least 61%.

35. The method of any one of claims 1-34, wherein the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6.
36. The method of any one of claims 1-35, wherein the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof comprising a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 7 and/or a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 8.
37. The method of any one of claims 1-35, wherein the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof comprising a full-length heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 9 and/or a full-length light chain (LC) comprising the amino acid sequence of SEQ ID NO: 10.
38. The method of any one of claims 1-37, wherein the ADC comprises a monoclonal anti-BCMA antibody or antigen-binding fragment thereof.
39. The method of any one of claims 1-38, wherein the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that is a full-length antibody.
40. The method of any one of claims 1-38, wherein the ADC comprises an anti-BCMA antibody or antigen-binding fragment thereof that is an antigen binding fragment.
41. The method of claim 40, wherein the antigen binding fragment comprises a single chain Fv (scFv).

42. The method of any one of claims 1-41, wherein the cytotoxin is SG3249.
43. The method of any one of claims 1-42, wherein the administration is intravenous.
44. The method of any one of claims 1-42, wherein the administration is intraperitoneal.
45. The method of any one of claims 1-42, wherein the administration is subcutaneous.
46. A method of treating Multiple Myeloma (MM) in a subject, the method comprising intravenously administering 0.14 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) every 3 weeks, wherein the ADC comprises:
 - (a) an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6;
 - (b) a protease-cleavable linker; and
 - (c) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer.
47. A method of treating Multiple Myeloma (MM) in a subject, the method comprising intravenously administering 0.14 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) every 6 weeks, wherein the ADC comprises:
 - (a) an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ

ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6;

(b) a protease-cleavable linker; and

(c) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer.

48. A method of treating Multiple Myeloma (MM) in a subject, the method comprising intravenously administering 0.14 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) every 3 weeks for 2 cycles, and then intravenously administering 0.07 mg/kg of the ADC every 6 weeks, wherein the ADC comprises:

(a) an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6;

(b) a protease-cleavable linker; and

(c) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer.

49. A method of treating Multiple Myeloma (MM) in a subject, the method comprising intravenously administering 0.10 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA) every 3 weeks for at least 6 months, wherein the ADC comprises:

(a) an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1) amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ

ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6;

(b) a protease-cleavable linker; and

(c) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer.

50. The method of any one of claims 1-49, wherein the subject has been pre-treated with daratumumab.
51. The method of any one of claims 1-50, wherein the administration results in a response in the subject for a duration of at least 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months.
52. The method of any one of claims 1-51, further comprising administration of one or more additional therapeutic agents.
53. The method of claim 52, wherein the additional therapeutic agent is Daratumumab.
54. The method of claim 52, wherein the additional therapeutic agents are Lenalidomide and dexamethasone.
55. The method of any one of claims 52 to 54, wherein the ADC and the one or more additional therapeutic agents are administered simultaneously or sequentially.
56. A method of treating Multiple Myeloma (MM) in a subject, the method comprising administering to the subject about 0.0125 mg/kg to about 0.2 mg/kg of an antibody-drug conjugate (ADC) directed against B-Cell Maturation Antigen (BCMA),
wherein the ADC comprises:
 - (a) an anti-BCMA antibody or antigen-binding fragment thereof comprising (a) a heavy chain variable region comprising a complementarity determining region 1 (HCDR1)

amino acid sequence of SEQ ID NO: 1, an HCDR2 amino acid sequence of SEQ ID NO: 2, and an HCDR3 amino acid sequence of SEQ ID NO: 3 and (b) a light chain variable region comprising a complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, an LCDR2 amino acid sequence of SEQ ID NO: 5, and an LCDR3 amino acid sequence of SEQ ID NO: 6;

(b) a protease-cleavable linker; and

(c) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer, and wherein

$\geq 80\%$ of bone marrow plasma cells obtained from the subject are CD138+ and BCMA+.

57. The method of any one of claims 46 to 56, wherein the pyrrolobenzodiazepine (PBD) dimer is SG3249.

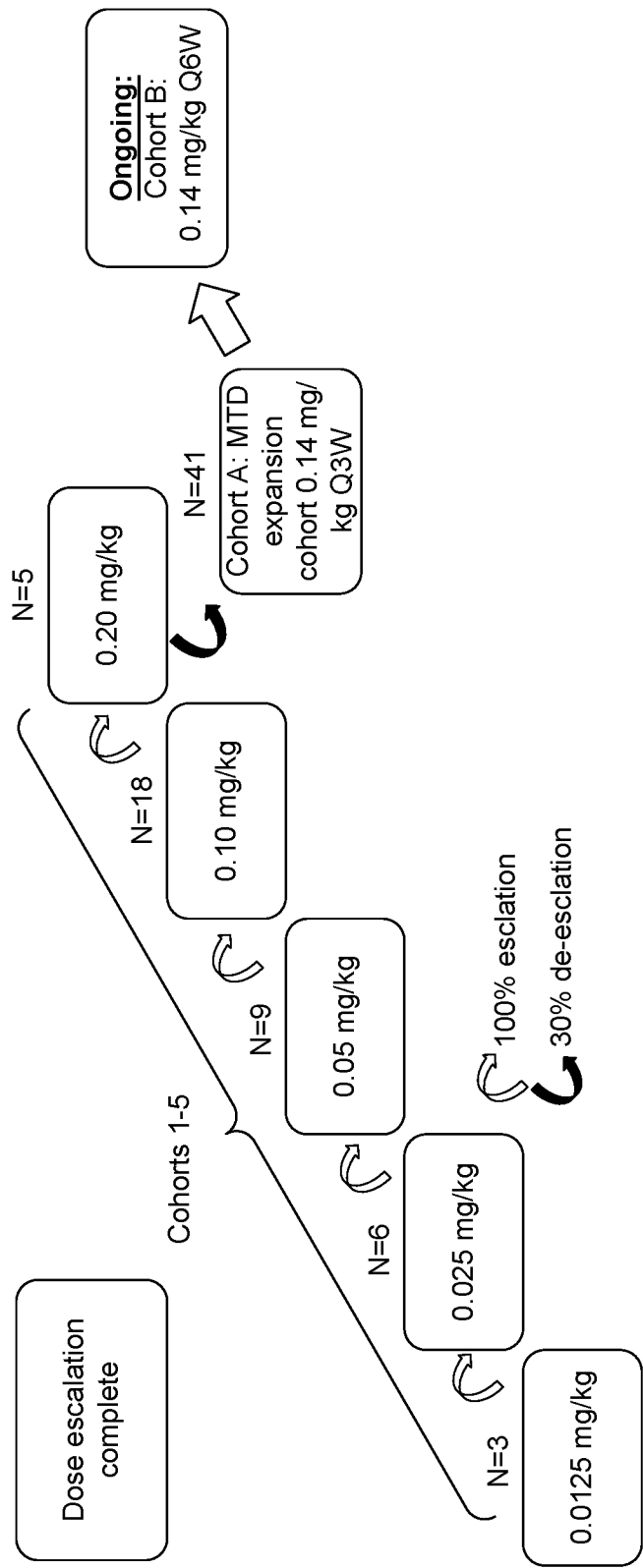


FIG. 1

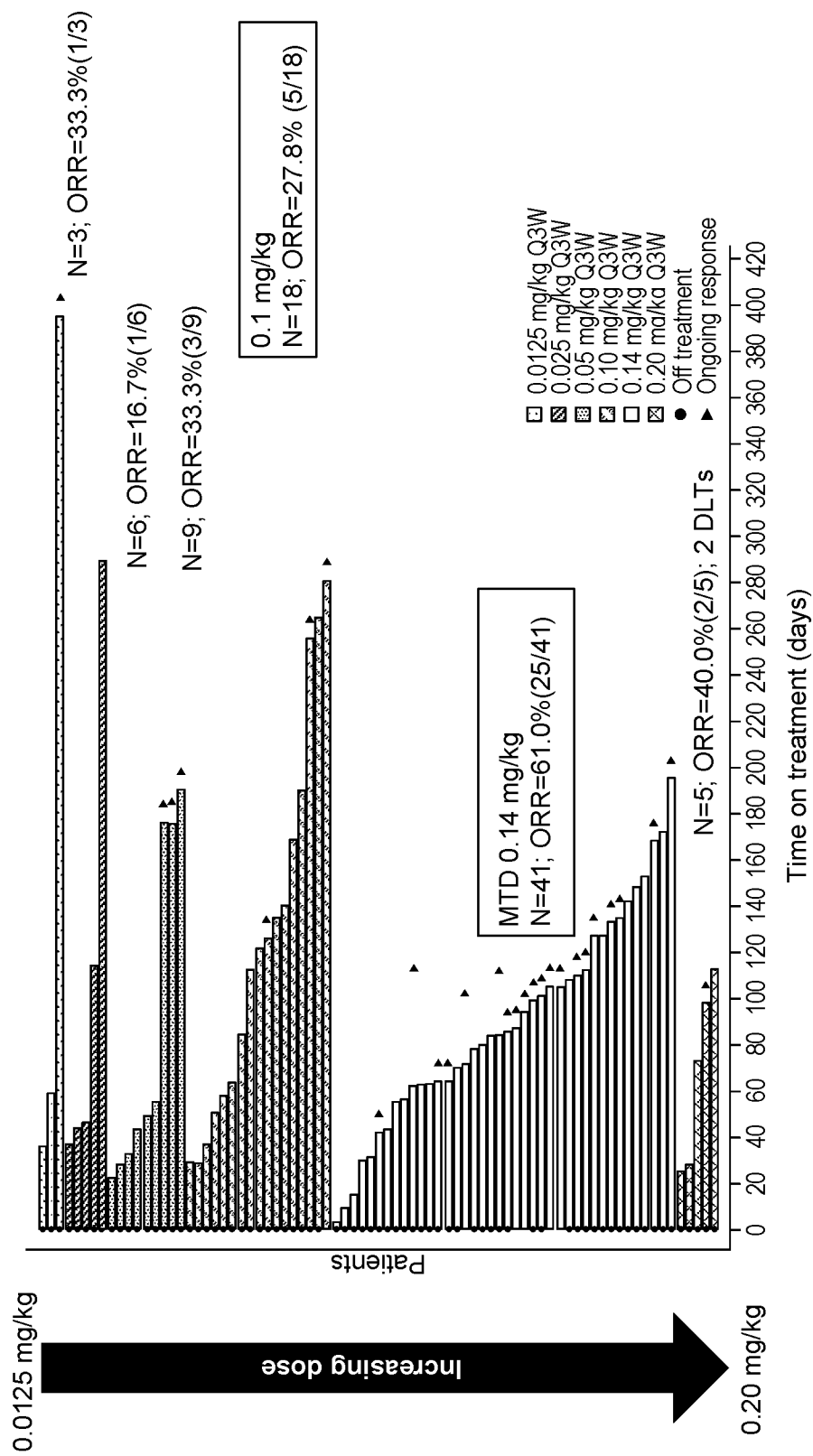


FIG. 2

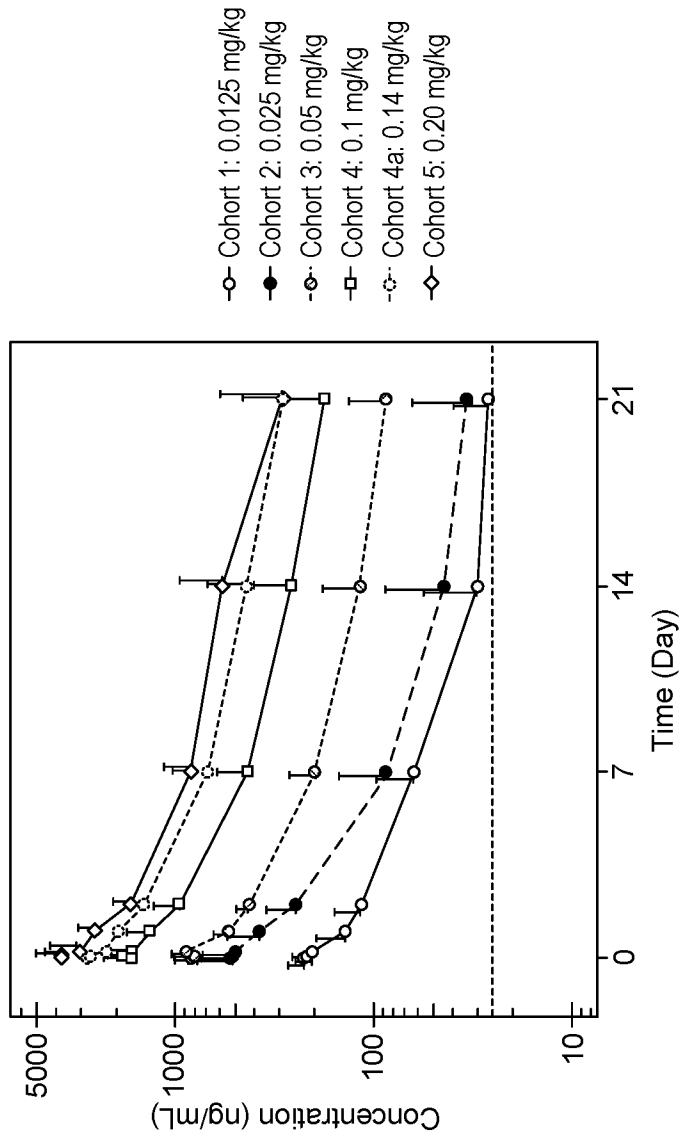


FIG. 3

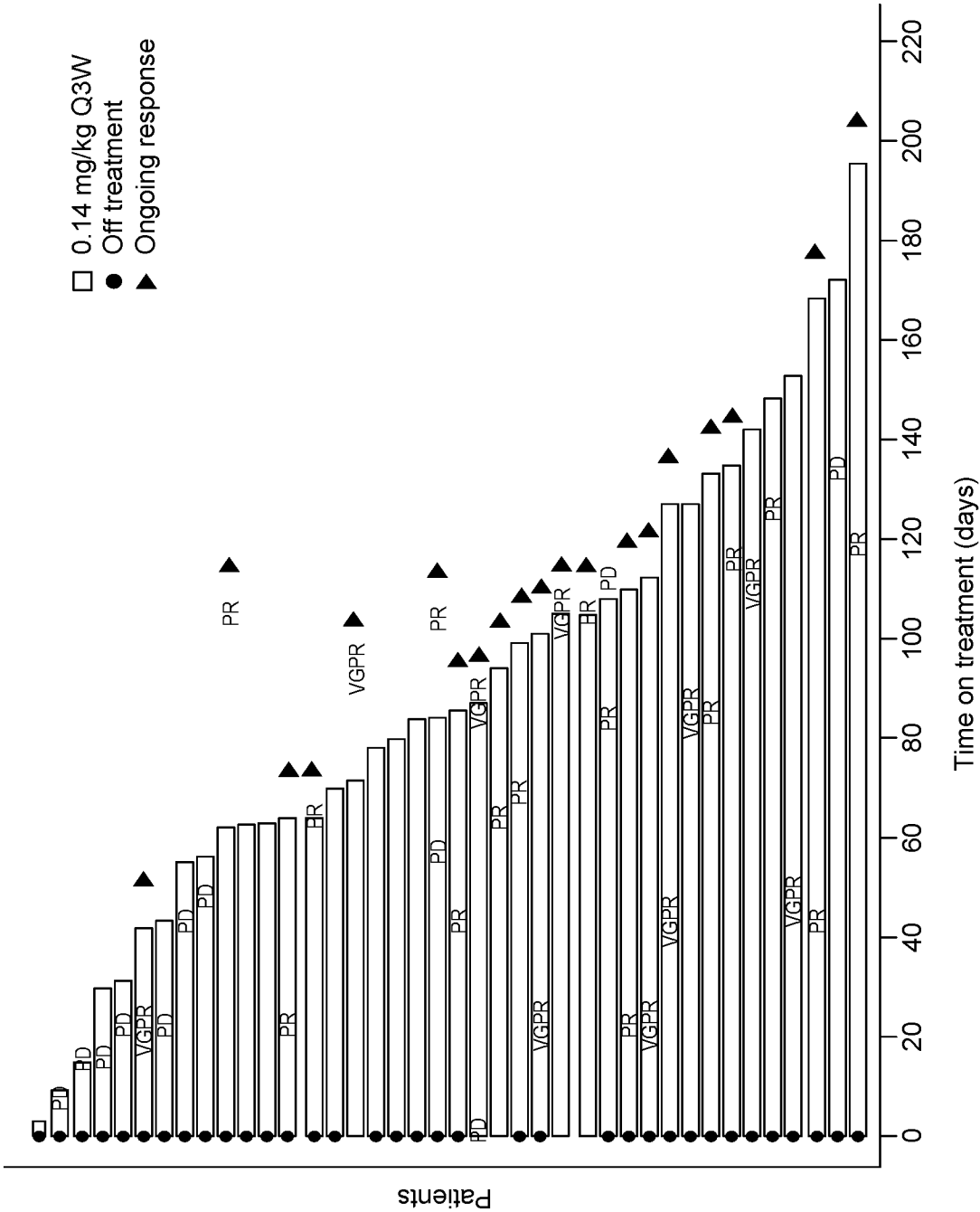


FIG. 4

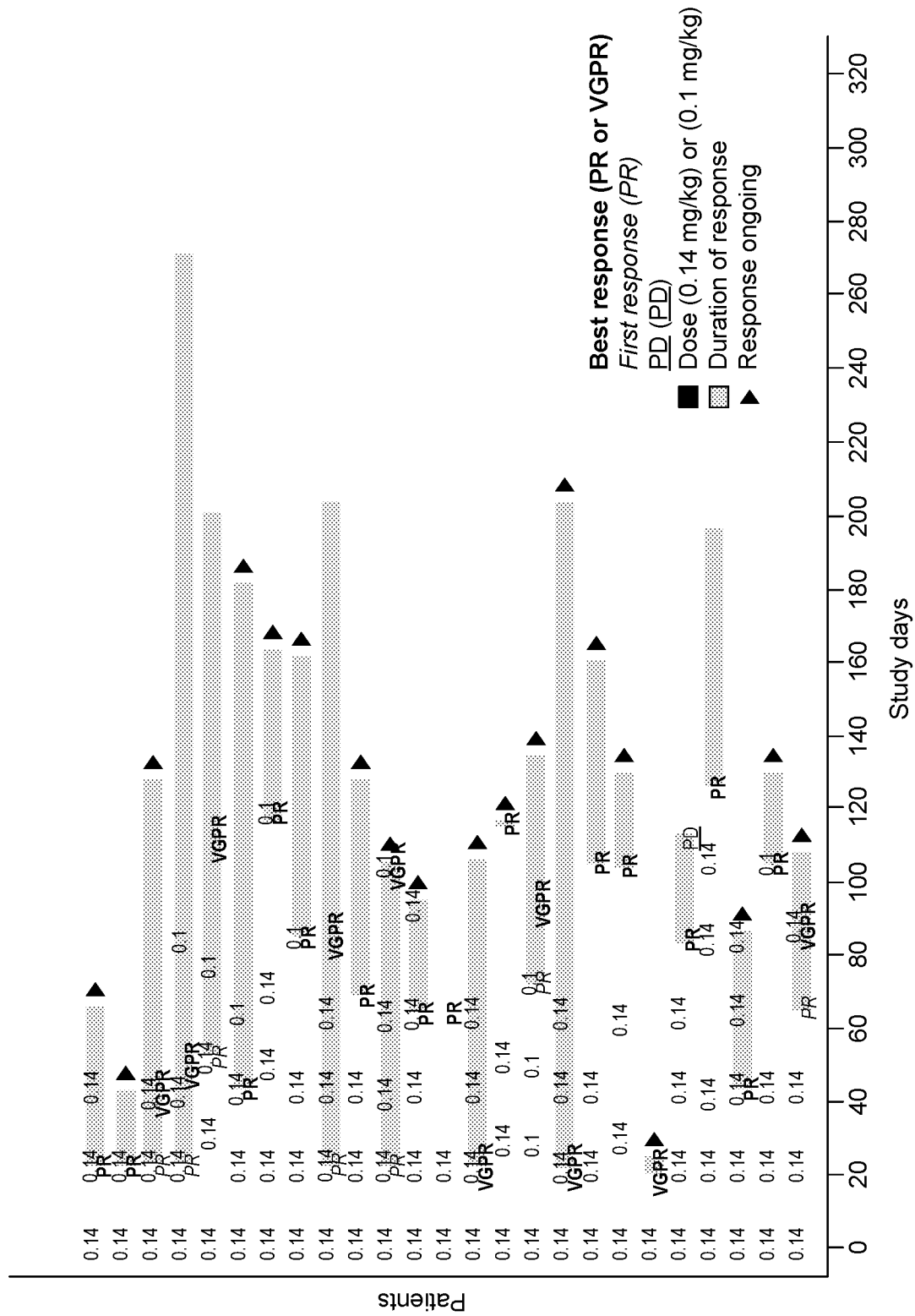


FIG. 5

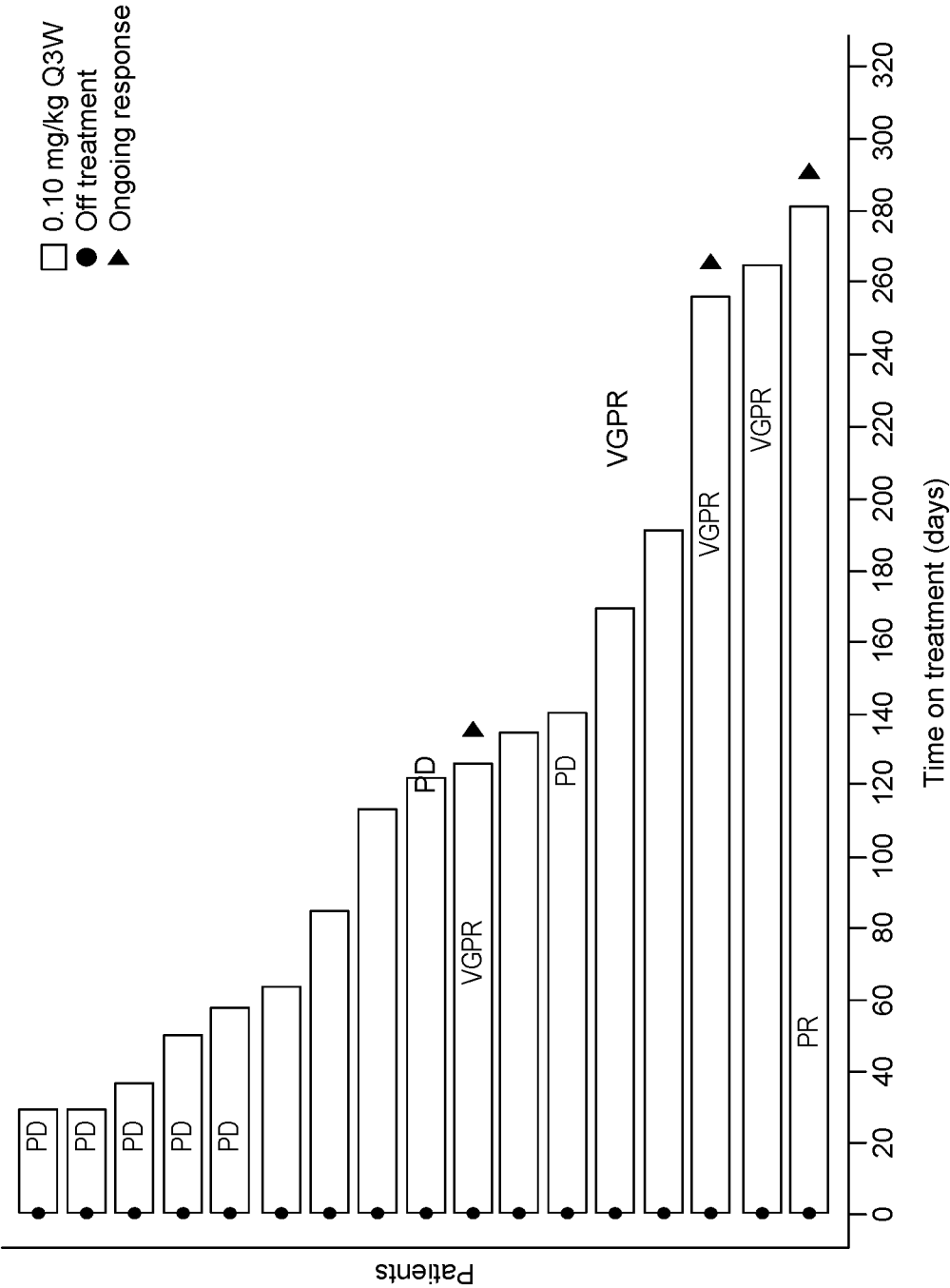


FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2021/060187

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/395; A61K 47/68; A61P 35/00; C07K 16/30; C07K 19/00; C12N 15/62 (2022.01)

CPC - A61K 39/39558; A61K 47/6803; A61K 47/6849; A61K 47/6867; A61K 2039/505; A61P 35/00; C07K 2317/565; C07K 2317/732 (2022.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

see Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

see Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

see Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2019/0040152 A1 (MEDIMMUNE LLC) 07 February 2019 (07.02.2019) entire document	1-3, 6 --- 4, 46-49, 56
Y	US 2014/0161828 A1 (AMGEN INC.) 12 June 2014 (12.06.2014) entire document	4
Y	US 2016/0250346 A1 (MEDIMMUNE LIMITED et al) 01 September 2016 (01.09.2016) entire document	46-49, 56
A	US 2016/0130362 A1 (GENMAB A/S) 12 May 2016 (12.05.2016) entire document	1-6, 46-49, 56

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

07 January 2022

Date of mailing of the international search report

JAN 31 2022

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Harry Kim

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2021/060187

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:
 SEQ ID NOs: 1-6 were searched.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2021/060187

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 7-45, 50-55, 57
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.