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- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

(54) Title: DOSING REGIMEN FOR COMBINATION THERAPIES WITH MULTISPECIFIC ANTIBODIES TARGETING B-CELL MATURATION ANTIGEN AND GAMMA SECRETASE INHIBITORS

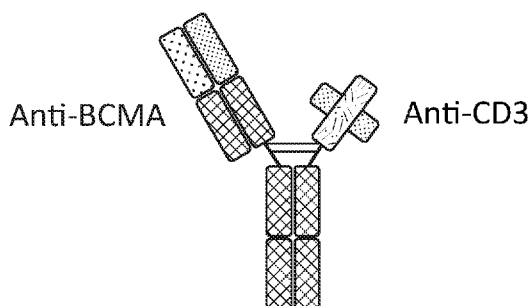


FIG. 1

(57) Abstract: The present disclosure relates to dosing regimens, formulations, and combinations comprising a multispecific antibody having at least binding specificity towards B cell maturation antigen (BCMA) and a T-cell engaging arm; and methods of using such multispecific antibodies in the treatment or prevention of disease, such as, cancer.

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**DOSING REGIMEN FOR COMBINATION THERAPIES WITH MULTISPECIFIC
ANTIBODIES TARGETING B-CELL MATURATION ANTIGEN AND GAMMA SECRETASE
INHIBITORS**

5 **1. CROSS-REFERENCE TO RELATED APPLICATIONS**

 This application claims the priority benefit of U.S. provisional application no. 63/109,907, filed November 5, 2020, the contents of which are incorporated herein by reference in its entirety.

2. SEQUENCE LISTING

10 The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. The ASCII copy, created on October 1, 2021, is named PAT058995-WO-PCT_SL.txt and is 15,435 bytes in size.

3. INCORPORATION BY REFERENCE

15 All publications, patents, patent applications and other documents cited in this application are hereby incorporated by reference in their entireties for all purposes to the same extent as if each individual publication, patent, patent application or other document were individually indicated to be incorporated by reference for all purposes. In the event that there are any inconsistencies between the teachings of one or more of the references incorporated
20 herein and the present disclosure, the teachings of the present specification are intended.

4. BACKGROUND

 BCMA is a tumor necrosis family receptor (TNFR) member expressed on cells of the B-cell lineage. BCMA expression is the highest on terminally differentiated B cells that assume the long lived plasma cell fate, including plasma cells, plasmablasts and a subpopulation of
25 activated B cells and memory 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. Cancers with increased expression of BCMA include some hematological cancers, such as multiple myeloma, Hodgkin's and non-Hodgkin's lymphoma, various leukemias, and glioblastoma.

30 Various BCMA binding molecules are in clinical development, including BCMA antibody-drug conjugates such as GSK2857916 (GlaxoSmithkline) and bispecific BCMA binding molecules targeting BMCA and CD3 such as PF06863135 (Pfizer), EM 901 (EngMab), JNJ-64007957 (Janssen), and AMG 420 (Amgen). See, Cho *et al.*, 2018, Front Immunol. 9:1821; WO 2016/0166629.

35 Further, membrane bound BCMA (mBCMA) on a surface on multiple myeloma cells is modulated by gamma-secretase (GS), resulting in release of a soluble BCMA (sBCMA)

fragment composed of the extracellular domain and part of the transmembrane region. See, Laurent, Sarah *et al.*, 2015, Nat. Comm. GS-mediated cleavage of mBCMA may limit efficacy of BCMA-directed antibodies both by lowering target antigen density and providing a soluble decoy that could bind to the BCMA-directed antibodies and increase target-mediated clearance.

5 One of the primary safety concerns of any antibody-based drugs, including CD3 bispecific molecules, is its potential to induce life-threatening side effects such as cytokine release syndrome ("CRS"). See, Shimabukuro-Vornhagen *et al.*, 2018, J. Immunother Cancer. 6:56.

10 Thus, there is an unmet medical need for polypeptides, *e.g.*, antibodies and multispecific binding molecules, which bind BCMA, and which have an improved safety profile (*e.g.*, decreasing cytokine release) while still retaining a high efficacy.

15 Further, there is an unmet medical need for the proper dosing of antibodies and multispecific binding molecules, which bind BCMA, in order to reduce the chances of producing unwanted side effects, including CRS. There is also an unmet need in order to reduce the total amount of antibodies and multispecific binding molecules (and potentially unwanted side effects) without comprising efficacy.

5. SUMMARY

20 Disclosed herein, inter alia, are methods of using, and formulations, combinations, and compositions comprising a B cell maturation antigen (BCMA) binding molecule (*e.g.*, a multispecific antibody, which can be an immunoglobulin-based multispecific binding molecule (MBM) described herein, or *e.g.*, a CAR-T and/or a RLT). In some cases, the BCMA binding molecule that has the ability to target BCMA expressing cells and also the ability to engage a T-cell (*e.g.*, by having a CD3 binding arm). The methods, formulations, combinations and compositions are exemplified by a BCMA binding molecule referred to herein as BSBM3. Thus, 25 references to a "BCMA binding molecule" also apply to BSBM3.

30 Disclosed herein is a method of treating a subject suffering from cancer (*e.g.*, multiple myeloma) comprising administering to the subject one or more treatment doses of a B-cell maturation antigen (BCMA) binding molecule and a gamma secretase inhibitor (GSI). In some embodiments, the GSI is administered at a dose of about 0.1 mg to about 10 mg. In some 30 embodiments, the GSI is administered to the subject at least once a week.

 In some embodiments, the GSI is administered at a dose of about 0.9 mg. In some embodiments, the GSI is administered at a dose of about 2 mg. In some embodiments, the GSI is administered at a dose of about 4 mg. In some embodiments, the GSI is administered at a dose of about 6 mg.

In some embodiments, the GSi is administered twice a week, as a first GSi dose and a second GSi dose. In some embodiments, the first GSi dose and the second GSi dose are administered on two consecutive days. In some embodiments, the first GSi dose and the second GSi dose are administered on the same day. In some embodiments, the first GSi dose and the second GSi dose are administered on two non-consecutive days. In some embodiments, the first GSi dose is administered about 24 hours prior the second GSi dose. In some embodiments, after the second GSi dose is administered to the subject, the GSi is not readministered for at least 5 consecutive days. In some embodiments, the first GSi dose is administered to the subject one day before the BCMA binding molecule is administered. In some embodiments, the second GSi dose is administered to the subject on the same day as the BCMA binding molecule. In some embodiments, the first GSi dose is administered to the subject the day before the BCMA binding molecule is administered and the second GSi dose is administered to the subject on the next day along with the BCMA binding molecule. In some embodiments, the second GSi dose is administered to the subject about 2 hours prior to the administration of the BCMA binding molecule.

The GSi doses can be administered in various forms. For example, the GSi can be administered as an oral capsule. In some embodiments, the GSi is LY-450139, PF-5212362, BMS-708163, MK-0752, ELN-318463, BMS-299897, LY-411575, DAPT, AL-101 (BMS-906024), AL-102 (BMS-986115), PF-3084014, RO4929097, LY3039478, or any combination thereof. For example, in some embodiments, the GSi is AL-102 also known as BMS-986115.

The BCMA binding molecule can be any molecule that specifically targets BCMA expressing cells. For example, the BCMA binding molecule can be an antibody, radioligand therapy (RLT), or chimeric antigen receptor T cell therapy (CAR-T). In some embodiments, the BCMA binding molecule is an antibody. For example, in some embodiments, the BCMA binding molecule is a bispecific antibody. In embodiments, where the BCMA binding molecule is a bispecific antibody, the bispecific antibody can in some cases bind to human BCMA and human CD3. In these embodiments, the bispecific antibody that binds to human BCMA and human CD3 can comprise (a) a first polypeptide whose amino acid sequence comprises the amino acid sequence of SEQ ID NO:1; (b) a second polypeptide whose amino acid sequence comprises the amino acid sequence of SEQ ID NO:2; and (c) a third polypeptide whose amino acid sequence comprises the amino acid sequence of SEQ ID NO:3.

In some embodiments, the BCMA binding molecule is a bispecific antibody that is dosed at between about 1 µg/kg to 600 µg/kg. In some embodiments, the BCMA binding molecule is a bispecific antibody that is dosed at least at 12 µg/kg. In some embodiments, the BCMA bispecific antibody is administered to the subject at a dose of about 6 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 0.9 mg. In some embodiments, the BCMA bispecific antibody is administered to the subject at a dose of about

12 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 0.9 mg. In some embodiments, the BCMA bispecific antibody is administered to the subject at a dose of about 12 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 2 mg. In some embodiments, the BCMA bispecific antibody is administered to the subject at a dose of about 24 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 2 mg. In some embodiments, the BCMA bispecific antibody is administered to the subject at a dose of about 48 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 2 mg. In some embodiments, the BCMA bispecific antibody is administered to the subject at a dose of about 48 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 4 mg. In some embodiments, the BCMA bispecific antibody is administered to the subject at a dose of about 96 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 4 mg. In some embodiments, the BCMA bispecific antibody is administered to the subject at a dose of about 192 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 4 mg. In some embodiments, the BCMA bispecific antibody is administered to the subject at a dose of about 384 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 4 mg. In some embodiments, the BCMA bispecific antibody is administered to the subject at a dose of about 384 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 6 mg.

20 In some embodiments, the BCMA binding molecule is a CAR-T. In some embodiments, the BCMA binding molecule is RLT.

In some embodiments, the method described throughout is repeated until the subject is in remission. In some embodiments, the remission is complete or partial remission.

In some embodiments, the subject has measurable disease. For example, the subject (a) has serum M-protein levels of ≥ 1 g / dL; (b) produces urine M-protein levels of ≥ 200 mg / 24 hours; and/or (c) has serum free light chain (sFLC) levels of at least 100 mg / L of involved FLC.

In some embodiments, the multiple myeloma is relapsed. In some embodiments, the multiple myeloma is refractory.

30 In some embodiments, the BCMA binding molecule is administered to the subject intravenously. In some embodiments, the BCMA binding molecule is administered to the subject as an infusion. In some embodiments, the infusion can be performed over a 1.5 – 3 hour span. In some embodiments, the infusion is over a 2 hour span.

In some embodiments, the method comprises prior to administering the first treatment dose of the BCMA binding molecule, administering a priming dose of the BCMA binding molecule to the subject. In some embodiments, the priming dose is less than the first BCMA

binding molecule dose. In some embodiments, the priming dose is equal to the first BCMA binding molecule dose.

In some embodiments, the priming dose is initiated one week prior to administering the first BCMA binding molecule dose. In some embodiments, the priming dose is divided. In some embodiments, the priming dose is administered over a period of two days. In some embodiments, less than half the priming dose is administered on the first day and the remainder of the priming dose is administered on the second day. In some embodiments, about a third of the priming dose is administered on the first day and about two thirds of the priming dose is administered on the second day.

In some embodiments, the method further comprises administering to the subject one or more additional therapeutic agents. For example, the additional therapeutic agents can be antidiarrheals (e.g., loperamide), octreotide, glucocorticoids (e.g, prednisone, cortisone, dexamethasone), emollients, antibiotics, paracetamol, acetaminophen, antihistamines, anti-T cell directed therapy, or any combination thereof. In some embodiments, the one or more additional therapeutic agents reduces a side effect of the GSi and/or the BCMA binding molecule. In some embodiments, the side effect is cytokine release syndrome (CRS). In some embodiments, the additional therapeutic agent is a glucocorticoid. For example, the glucocorticoid can be dexamethasone or methylprednisolone. In some embodiments, glucocorticoid is dexamethasone and is administered at a dose of about 8 mg to about 10 mg daily. In some embodiments, the glucocorticoid is methylprednisolone and is administered at a dose of at least about 2 mg/kg.

In some embodiments, the additional therapeutic agent is an anti-T cell directed therapy. In some embodiments, the anti-T cell directed therapy is tocilizumab, canakinumab, or any combination thereof.

In some embodiments, the subject has been previously treated with at least two prior treatment regimens.

6. BRIEF DESCRIPTION OF THE FIGURES

FIG. 1: Format of the BCMA binding molecule designated as BSBM3.

FIGS. 2A-2C show BSBM3 mediated T cell proliferation, cytokine production and specific lysis of KMS11 myeloma cells via RTCC. Healthy donor T cells were co-cultured with KMS11 cells over-expressing luciferase at a 1:1 ratio in the presence of BSBM3 or non-targeting (NT) control antibody at the indicated concentrations. **FIG. 2A** shows levels of IFN γ and TNF α as measured by MSD assay with cell culture supernatants that were collected at 24 hr. **FIG. 2B** shows T cells counts as determined by CD3⁺ event counts using flow cytometry and normalized to counting beads controls after 4 days in coculture. **FIG. 2C** shows %RTCC (% lysis of KMS11 cells) as determined at 72 hr by the reduction in luciferase activity compared

to KMS11 cells alone. Mean values $\pm$ SEM are shown from three individual healthy donor T cells, each with three independent experiments (9 biological replicates total).

FIG. 3 shows that RTCC assay represents the most sensitive in vitro functional assays. EC30 values for BSBM3 were plotted for three different types of in vitro functional assays, RTCC, T cell proliferation and cytokine production (as shown in FIG. 2). Each data point represents one of nine biological replicates (T cells from three healthy donors were tested individually, each in three independent experiments).

FIG. 4 shows that soluble BCMA decreases the activity of BSBM3 in RTCC assay. The EC30 values for BSBM3 in RTCC assays with added soluble BCMA as indicated are shown. Each data point represents one of nine biological replicates (T cells from three healthy donor T cells were tested individually, each in three independent experiments).

FIG. 5 shows the anti-tumor activity of BSBM3 on KMS11 xenograft in a human PBMC adoptive transfer mouse model. NSG mice were inoculated with KMS11 cells via tail vein injection on Day 0 (D0), adoptively transferred with PBMCs on D7, and treated on D15 with the following doses of BSBM3: 0.03 mg/kg (triangle), 0.3 mg/kg (circle) or 3.0 mg/kg (diamond). For controls: tumor bearing mice without human PBMCs (increasing circles), tumor-bearing mice with human PBMCs but no Ab treatment (squares). The result from one representative experiment is shown from three biological replicates. * $p < 0.05$, Dunnett's multiple comparison test. Data are expressed as the geometric mean $\pm$ SEM from 5 mice per group.

FIG. 6 shows the clinical trial study schema for BSBM3.

FIG. 7 shows the international staging system for the BSBM3 clinical trial.

FIG. 8: **FIG 8A** shows that AL-102 treatment led to reduced sBCMA and increased mBCMA density on MM cell line KMS11 *in vitro*. Concentration of sBCMA levels (ng/mL) from the culture supernatants of KMS-11 cells treated for 20 hours with a serial dilution of AL-102 are shown on the left Y-axis. Cell surface mBCMA density is represented by Antibody Binding Capacity (ABC) using anti-BCMA (clone 19F2) on the surface of these AL-102 treated KMS-11 cells is shown on the right Y-axis. EC50 values are calculated by using a sigmoidal, 4-parameter non-linear regression curve fit. **FIG. 8B** shows a time course of sBCMA and mBCMA levels following the administration of AL-102. NSG mice with established subcutaneous tumors from KMS11 cells were dosed with AL-102 for 5 doses (first dose at 0 hr and last dose at 48 hr). Levels of sBCMA (ng/mL) from the serum at the indicated time points were measured by ELISA (closed circles, left Y-axis) whereas mBCMA levels on tumor cells were measured by flow cytometry and shown as MFI (open squares, right Y-axis)

FIG. 9 shows BSBM3 EC50 (mean+/-SEM) with increasing concentrations of AL-102: 1000 nM serially diluted 5-fold across 8-points. T-cell donor n=3. AL-102 enhanced the RTCC potency of BSBM3 in a dose dependent manner.

FIG. 10 shows BSBM3 mediated RTCC activity assayed in the presence of 8nM BSBM3. BSBM3 was added at 1:5 serial dilutions across ten points starting from 10 nM. The average RTCC activity (mean+/-SEM) from three independent RTCC assays (using three different healthy donor T cells) were plotted against BSBM3 concentrations in the presence of 8nM BSBM3.

FIG. 11 shows the different dose levels of the BCMA binding molecule in combination with the proposed GSi.

7. DETAILED DESCRIPTION

While some embodiments have been/will be shown and described throughout, such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein will be employed in practicing the invention.

The present disclosure provides methods of treating and/or preventing a disease (e.g., cancer) comprising administering to a subject in need thereof a composition comprising a BCMA binding molecule, particularly the BCMA binding molecule designated as BSBM3, as well as a gamma secretase inhibitor (GSi). In some aspects, the methods further comprise administering one or more therapeutic agents, e.g., one or more anti-tumor agents. The disclosure further provides formulations, dosing, dosing regimens and schedules, biomarkers, pharmaceutical combinations, and other relevant clinical features.

According to the present disclosure, additional therapeutic agents that can be used in combination with a BCMA binding molecule such as BSBM3 and GSi, include but are not limited to, an inhibitor of an inhibitory molecule (e.g., a checkpoint inhibitor), an activator of a costimulatory molecule, a chemotherapeutic agent, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, or any of the therapeutic agents disclosed herein. In some embodiments, the one or more therapeutic agents can be a PD-1 inhibitor, a LAG-3 inhibitor, a cytokine, an A2A antagonist, a GITR agonist, a TIM-3 inhibitor, a STING agonist, and a TLR7 agonist, for treating and/or preventing a patient/subject with cancer.

The details of the disclosure are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular

forms also include the plural unless the context clearly dictates otherwise. 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 belongs.

7.1. Definitions

5 As used herein, the following terms are intended to have the following meanings:

ADCC: By “ADCC” or “antibody dependent cell-mediated cytotoxicity” as used herein is meant the cell-mediated reaction where nonspecific cytotoxic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause lysis of the target cell. ADCC is correlated with binding to FcγRIIIa; increased binding to FcγRIIIa leads to an increase
10 in ADCC activity.

ADCP: By “ADCP” or antibody dependent cell-mediated phagocytosis as used herein is meant the cell-mediated reaction where nonspecific phagocytic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause phagocytosis of the target cell.

15 **Additional Agent:** For convenience, an agent that is used in combination with an antigen-binding molecule of the disclosure is referred to herein as an “additional” agent.

Antibody: The term “antibody” as used herein refers to a polypeptide (or set of polypeptides) of the immunoglobulin family that is capable of binding an antigen non-covalently, reversibly and specifically. For example, a naturally occurring “antibody” of the IgG type is a
20 tetramer comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain
25 constant region is comprised of one domain (abbreviated herein as CL). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3,
30 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 can 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. The term “antibody” includes, but is not limited to, monoclonal antibodies, human antibodies, humanized
35 antibodies, camelised antibodies, chimeric antibodies, bispecific or multispecific antibodies and anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the

disclosure). The antibodies can be of any isotype/class (e.g., IgG, IgE, IgM, IgD, IgA and IgY) or subclass (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2).

Both the light and heavy chains are divided into regions of structural and functional homology. The terms “constant” and “variable” are used functionally. In this regard, it will be appreciated that the variable domains of both the light (VL) and heavy (VH) chain portions determine antigen recognition and specificity. Conversely, the constant domains of the light chain (CL) and the heavy chain (CH1, CH2 or CH3) confer important biological properties such as secretion, transplacental mobility, Fc receptor binding, complement binding, and the like. By convention the numbering of the constant region domains increases as they become more distal from the antigen-binding site or amino-terminus of the antibody. In a wild-type antibody, at the N-terminus is a variable region and at the C-terminus is a constant region; the CH3 and CL domains actually comprise the carboxy-terminus of the heavy and light chain, respectively.

Antibody fragment: The term “antibody fragment” of an antibody as used herein refers to one or more portions of an antibody. In some embodiments, these portions are part of the contact domain(s) of an antibody. In some other embodiments, these portion(s) are antigen-binding fragments that retain the ability of binding an antigen non-covalently, reversibly and specifically, sometimes referred to herein as the “antigen-binding fragment”, “antigen-binding fragment thereof,” “antigen-binding portion”, and the like. Examples of binding fragments include, but are not limited to, single-chain Fvs (scFv), a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab)2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a dAb fragment (Ward *et al.*, 1989, Nature 341:544-546), which consists of a VH domain; and an isolated complementarity determining region (CDR). Thus, the term “antibody fragment” encompasses both proteolytic fragments of antibodies (e.g., Fab and F(ab)2 fragments) and engineered proteins comprising one or more portions of an antibody (e.g., an scFv).

Antibody fragments can also be incorporated into single domain antibodies, maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, e.g., Hollinger and Hudson, 2005, Nature Biotechnology 23: 1126-1136). Antibody fragments can be grafted into scaffolds based on polypeptides such as Fibronectin type III (Fn3) (see U.S. Pat. No. 6,703,199, which describes fibronectin polypeptide monobodies).

Antibody fragments can be incorporated into single chain molecules comprising a pair of tandem Fv segments (for example, VH-CH1-VH-CH1) which, together with complementary light chain polypeptides (for example, VL-VC-VL-VC), form a pair of antigen-binding regions (Zapata *et al.*, 1995, Protein Eng. 8:1057-1062; and U.S. Pat. No. 5,641,870).

Antibody Numbering System: In the present specification, the references to numbered amino acid residues in antibody domains are based on the EU numbering system unless otherwise specified. This system was originally devised by Edelman *et al.*, 1969, Proc. Nat'l Acad. Sci. USA 63:78-85 and is described in detail in Kabat *et al.*, 1991, in Sequences of
5 Proteins of Immunological Interest, US Department of Health and Human Services, NIH, USA.

Antigen-binding domain: The term "antigen-binding domain" or "ABD" refers to a portion of an antigen-binding molecule that has the ability to bind to an antigen non-covalently, reversibly and specifically. Exemplary ABDs include antigen-binding fragments and portions of both immunoglobulin and non-immunoglobulin based scaffolds that retain the ability of binding
10 an antigen non-covalently, reversibly and specifically. As used herein, the term "antigen-binding domain" encompasses antibody fragments that retain the ability of binding an antigen non-covalently, reversibly and specifically.

Antigen-binding domain chain or ABD chain: Individual ABDs can exist as one (*e.g.*, in the case of an scFv) polypeptide chain or form through the association of more than one
15 polypeptide chains (*e.g.*, in the case of a Fab). As used herein, the term "ABD chain" refers to all or a portion of an ABD that exists on a single polypeptide chain. The use of the term "ABD chain" is intended for convenience and descriptive purposes only and does not connote a particular configuration or method of production.

Antigen-binding fragment: The term "antigen-binding fragment" of an antibody refers
20 to a portion of an antibody that retains has the ability to bind to an antigen non-covalently, reversibly and specifically.

Antigen-binding molecule: The term "antigen-binding molecule" refers to a molecule comprising one or more antigen-binding domains, for example an antibody. The antigen-binding molecule can comprise one or more polypeptide chains, *e.g.*, one, two, three, four or
25 more polypeptide chains. The polypeptide chains in an antigen-binding molecule can be associated with one another directly or indirectly (for example a first polypeptide chain can be associated with a second polypeptide chain which in turn can be associated with a third polypeptide chain to form an antigen-binding molecule in which the first and second polypeptide chains are directly associated with one another, the second and third polypeptide chains are
30 directly associated with one another, and the first and third polypeptide chains are indirectly associated with one another through the second polypeptide chain).

Associated: The term "associated" in the context of domains or regions within an antigen-binding molecule refers to a functional relationship between two or more polypeptide chains and/or two or more portions of a single polypeptide chain. In particular, the term
35 "associated" means that two or more polypeptides (or portions of a single polypeptide) are associated with one another, *e.g.*, non-covalently through molecular interactions and/or

covalently through one or more disulfide bridges or chemical cross-linkages, so as to produce a functional antigen-binding domain. Examples of associations that might be present in an antigen-binding molecule include (but are not limited to) associations between Fc regions in an Fc domain, associations between VH and VL regions in a Fab or Fv, and associations between CH1 and CL in a Fab.

B cell: As used herein, the term “B cell” refers to a cell of B cell lineage, which is a type of white blood cell of the lymphocyte subtype. Examples of B cells include plasmablasts, plasma cells, lymphoplasmacytoid cells, memory B cells, follicular B cells, marginal zone B cells, B-1 cells, B-2 cells, and regulatory B cells.

B cell malignancy: As used herein, a B cell malignancy refers to an uncontrolled proliferation of B cells. Examples of B cell malignancy include non-Hodgkin’s lymphomas (NHL), Hodgkin’s lymphomas, leukemia, and myeloma. For example, a B cell malignancy can be, but is not limited to, multiple myeloma, chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), follicular lymphoma, mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), marginal zone lymphomas, Burkitt lymphoma, lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia), hairy cell leukemia, primary central nervous system (CNS) lymphoma, primary mediastinal large B-cell lymphoma, mediastinal grey-zone lymphoma (MGZL), splenic marginal zone B-cell lymphoma, extranodal marginal zone B-cell lymphoma of MALT, nodal marginal zone B-cell lymphoma, and primary effusion lymphoma, and plasmacytic dendritic cell neoplasms.

BCMA: As used herein, the term “BCMA” refers to B-cell maturation antigen. BCMA (also known as TNFRSF17, BCM or CD269) is a member of the tumor necrosis receptor (TNFR) family and is predominantly expressed on terminally differentiated B cells, e.g., memory B cells and plasma cells. Its ligands include B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL). The protein BCMA is encoded by the gene TNFRSF17. Exemplary BCMA sequences are available at the Uniprot database under accession number Q02223.

BCMA binding molecule: The term “BCMA binding molecule” refers to a molecule that specifically binds to BCMA, particularly human BCMA. Examples of BCMA binding molecules including multispecific binding molecules that comprise at least one ABD that binds to BCMA, e.g., multispecific antibodies, bispecific antibodies and other bispecific binding molecules. A particular BCMA binding molecule of the disclosure is referred to herein as BSBM3.

Bispecific binding molecule: The term “bispecific binding molecule” or “BBM” refers to a molecule that specifically binds to two antigens and comprises two or more ABDs. The BBMs of the disclosure comprise at least one antigen-binding domain which is specific for BCMA and at least one antigen-binding domain which is specific for a different antigen, e.g., component of

a TCR complex. Representative BBMs are illustrated in FIG. 1B-1AG. BBMs can comprise one, two, three, four or even more polypeptide chains.

Bivalent: The term “bivalent” as used herein in the context of an antigen-binding molecule refers to an antigen-binding molecule that has two ABDs. The domains can be the same or different. Accordingly, a bivalent antigen-binding molecule can be monospecific or bispecific. Bivalent BBMs comprise an ABD that specifically binds to BCMA and another ABD that binds to another antigen, e.g., a component of the TCR complex.

BSBM3: BSMB3 refers to a BCMA binding molecule comprising (a) a first polypeptide whose amino acid sequence comprises the amino acid sequence of SEQ ID NO:1; (b) a second polypeptide whose amino acid sequence comprises the amino acid sequence of SEQ ID NO:2; and (c) a third polypeptide whose amino acid sequence comprises the amino acid sequence of SEQ ID NO:3. When co-expressed, the first, second and third polypeptide associate to form a binding molecule with the configuration shown in FIG. 1.

Cancer: The term “cancer” refers to a disease characterized by the uncontrolled (and often rapid) growth of aberrant cells. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body. Examples of various cancers are described herein and include but are not limited to, leukemia, multiple myeloma, asymptomatic myeloma, Hodgkin’s lymphoma and non-Hodgkin’s lymphoma, e.g., any BCMA-positive cancers of any of the foregoing types. The term “cancerous B cell” refers to a B cell that is undergoing or has undergone uncontrolled proliferation

CD3: The term “CD3” or “cluster of differentiation 3” refers to the cluster of differentiation 3 co-receptor of the T cell receptor. CD3 helps in activation of both cytotoxic T-cell (e.g., CD8+ naïve T cells) and T helper cells (e.g., CD4+ naïve T cells) and is composed of four distinct chains: one CD3 γ chain (e.g., Genbank Accession Numbers NM_000073 and MP_000064 (human)), one CD3 δ chain (e.g., Genbank Accession Numbers NM_000732, NM_001040651, NP_00732 and NP_001035741 (human)), and two CD3 ϵ chains (e.g., Genbank Accession Numbers NM_000733 and NP_00724 (human)). The chains of CD3 are highly related cell-surface proteins of the immunoglobulin superfamily containing a single extracellular immunoglobulin domain. The CD3 molecule associates with the T-cell receptor (TCR) and ζ -chain to form the T-cell receptor (TCR) complex, which functions in generating activation signals in T lymphocytes. Unless expressly indicated otherwise, the reference to CD3 in the application can refer to the CD3 co-receptor, the CD3 co-receptor complex, or any polypeptide chain of the CD3 co-receptor complex.

Chimeric Antibody: The term “chimeric antibody” (or antigen-binding fragment thereof) is an antibody molecule (or antigen-binding fragment thereof) in which (a) the constant region, or a portion thereof, is altered, replaced or exchanged so that the antigen-binding site (variable

region) is linked to a constant region of a different or altered class, effector function and/or species, or an entirely different molecule which confers new properties to the chimeric antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, etc.; or (b) the variable region, or a portion thereof, is altered, replaced or exchanged with a variable region having a different or altered antigen specificity. For example, a mouse antibody can be modified by replacing its constant region with the constant region from a human immunoglobulin. Due to the replacement with a human constant region, the chimeric antibody can retain its specificity in recognizing the antigen while having reduced antigenicity in human as compared to the original mouse antibody.

Complementarity Determining Region: The terms “complementarity determining region” or “CDR,” as used herein, refer to the sequences of amino acids within antibody variable regions which confer antigen specificity and binding affinity. For example, in general, there are three CDRs in each heavy chain variable region (e.g., CDR-H1, CDR-H2, and CDR-H3) and three CDRs in each light chain variable region (CDR-L1, CDR-L2, and CDR-L3). The precise amino acid sequence boundaries of a given CDR can be determined using any one of a number of well-known schemes, including those described by Kabat *et al.*, 1991, “Sequences of Proteins of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (“Kabat” numbering scheme), Al-Lazikani *et al.*, 1997, JMB 273,927-948 (“Chothia” numbering scheme), or a combination thereof, and ImMunoGenTics (IMGT) numbering (Lefranc, 1999, The Immunologist, 7:132-136; Lefranc *et al.*, 2003, Dev. Comp. Immunol. 27, 55-77 (“IMGT” numbering scheme). In a combined Kabat and Chothia numbering scheme for a given CDR region (for example, HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 or LC CDR3), in some embodiments, the CDRs correspond to the amino acid residues that are defined as part of the Kabat CDR, together with the amino acid residues that are defined as part of the Chothia CDR. As used herein, the CDRs defined according to the “Chothia” number scheme are also sometimes referred to as “hypervariable loops.”

For example, under Kabat, the CDR amino acid residues in the heavy chain variable domain (VH) are numbered 31-35 (CDR-H1) (e.g., insertion(s) after position 35), 50-65 (CDR-H2), and 95-102 (CDR-H3); and the CDR amino acid residues in the light chain variable domain (VL) are numbered 24-34 (CDR-L1) (e.g., insertion(s) after position 27), 50-56 (CDR-L2), and 89-97 (CDR-L3). As another example, under Chothia, the CDR amino acids in the VH are numbered 26-32 (CDR-H1) (e.g., insertion(s) after position 31), 52-56 (CDR-H2), and 95-102 (CDR-H3); and the amino acid residues in VL are numbered 26-32 (CDR-L1) (e.g., insertion(s) after position 30), 50-52 (CDR-L2), and 91-96 (CDR-L3). By combining the CDR definitions of both Kabat and Chothia, the CDRs comprise or consist of, e.g., amino acid residues 26-35 (CDR-H1), 50-65 (CDR-H2), and 95-102 (CDR-H3) in human VH and amino acid residues 24-34 (CDR-L1), 50-56 (CDR-L2), and 89-97 (CDR-L3) in human VL. Under IMGT, the CDR amino

acid residues in the VH are numbered approximately 26-35 (CDR1), 51-57 (CDR2) and 93-102 (CDR3), and the CDR amino acid residues in the VL are numbered approximately 27-32 (CDR1), 50-52 (CDR2), and 89-97 (CDR3) (numbering according to "Kabat"). Under IMGT, the CDR regions of an antibody can be determined using the program IMGT/DomainGap Align.

- 5 Generally, unless specifically indicated, the antibody molecules can include any combination of one or more Kabat CDRs and/or Chothia CDRs.

Concurrently: The term "concurrently" is not limited to the administration of therapies (e.g., prophylactic or therapeutic agents) at exactly the same time, but rather it is meant that a pharmaceutical composition comprising an antigen-binding molecule is administered to a
10 subject in a sequence and within a time interval such that the molecules can act together with the additional therapy(ies) to provide an increased benefit than if they were administered otherwise.

Conservative Sequence Modifications: The term "conservative sequence modifications" refers to amino acid modifications that do not significantly affect or alter the
15 binding characteristics of a BCMA binding molecule or a component thereof (e.g., an ABD or an Fc region). Such conservative modifications include amino acid substitutions, additions and deletions. Modifications can be introduced into a BBM by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a
20 similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine,
25 methionine), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, one or more amino acid residues within a BBM can be replaced with other amino acid residues from the same side chain family and the altered BBM can be tested for, e.g., binding to target molecules and/or effective heterodimerization and/or effector function.

30 **Epitope:** An epitope, or antigenic determinant, is a portion of an antigen recognized by an antibody or other antigen-binding moiety as described herein. An epitope can be linear or conformational.

Effector Function: The term "effector function" refers to an activity of an antibody molecule that is mediated by binding through a domain of the antibody other than the antigen-binding domain, usually mediated by binding of effector molecules. Effector function includes
35 complement-mediated effector function, which is mediated by, for example, binding of the C1

component of the complement to the antibody. Activation of complement is important in the opsonization and lysis of cell pathogens. The activation of complement also stimulates the inflammatory response and may also be involved in autoimmune hypersensitivity. Effector function also includes Fc receptor (FcR)-mediated effector function, which can be triggered upon binding of the constant domain of an antibody to an Fc receptor (FcR). Binding of antibody to Fc receptors on cell surfaces triggers a number of important and diverse biological responses including engulfment and destruction of antibody-coated particles, clearance of immune complexes, ADCC, ADCP, release of inflammatory mediators, placental transfer and control of immunoglobulin production. An effector function of an antibody can be altered by altering, e.g., enhancing or reducing, the affinity of the antibody for an effector molecule such as an Fc receptor or a complement component. Binding affinity will generally be varied by modifying the effector molecule binding site, and in this case it is appropriate to locate the site of interest and modify at least part of the site in a suitable way. It is also envisaged that an alteration in the binding site on the antibody for the effector molecule need not alter significantly the overall binding affinity but can alter the geometry of the interaction rendering the effector mechanism ineffective as in non-productive binding. It is further envisaged that an effector function can also be altered by modifying a site not directly involved in effector molecule binding, but otherwise involved in performance of the effector function.

Fab: By “Fab” or “Fab region” as used herein is meant a polypeptide region that comprises the VH, CH1, VL, and CL immunoglobulin domain. These terms can refer to this region in isolation, or this region in the context of an antigen-binding molecule.

Fab domains are formed by association of a CH1 domain attached to a VH domain with a CL domain attached to a VL domain. The VH domain is paired with the VL domain to constitute the Fv region, and the CH1 domain is paired with the CL domain to further stabilize the binding module. A disulfide bond between the two constant domains can further stabilize the Fab domain.

Fab regions can be produced by proteolytic cleavage of immunoglobulin molecules (e.g., using enzymes such as papain) or through recombinant expression. In native immunoglobulin molecules, Fabs are formed by association of two different polypeptide chains (e.g., VH-CH1 on one chain associates with VL-CL on the other chain). The Fab regions are typically expressed recombinantly, typically on two polypeptide chains, although single chain Fabs are also contemplated herein.

Fc region: The term “Fc region” or “Fc chain” as used herein is meant the polypeptide comprising the CH2-CH3 domains of an IgG molecule, and in some cases, inclusive of the hinge. In EU numbering for human IgG1, the CH2-CH3 domain comprises amino acids 231 to 447, and the hinge is 216 to 230. Thus the definition of “Fc region” includes both amino acids

231-447 (CH2-CH3) or 216-447 (hinge-CH2-CH3), or fragments thereof. An "Fc fragment" in this context can contain fewer amino acids from either or both of the N- and C-termini but still retains the ability to form a dimer with another Fc region as can be detected using standard methods, generally based on size (e.g., non-denaturing chromatography, size exclusion chromatography). Human IgG Fc regions are of particular use in the present disclosure, and can be the Fc region from human IgG1, IgG2 or IgG4.

Fc domain: The term "Fc domain" refers to a pair of associated Fc regions. The two Fc regions dimerize to create the Fc domain. The two Fc regions within the Fc domain can be the same (such an Fc domain being referred to herein as an "Fc homodimer") or different from one another (such an Fc domain being referred to herein as an "Fc heterodimer").

Fv: The term "Fv", "Fv fragment" or "Fv region" refer to a region that comprises the VL and VH domains of an antibody fragment in a tight, noncovalent association (a VH-VL dimer). It is in this configuration that the three CDRs of each variable domain interact to define a target binding site. Often, the six CDRs confer target binding specificity to an antigen-binding molecule. However, in some instances even a single variable domain (or half of an Fv comprising only three CDRs specific for a target) can have the ability to recognize and bind target. In a native immunoglobulin molecule, the VH and VL of an Fv are on separate polypeptide chains but can be engineered as a single chain Fv (scFv). The terms also include Fvs that are engineered by the introduction of disulfide bonds for further stability.

The reference to a VH-VL dimer herein is not intended to convey any particular configuration. For example, in scFvs, the VH can be N-terminal or C-terminal to the VL (with the VH and VL typically connected by a linker as discussed herein).

Half Antibody: The term "half antibody" refers to a molecule that comprises at least one ABD or ABD chain and can associate with another molecule comprising an ABD or ABD chain through, e.g., a disulfide bridge or molecular interactions (e.g., knob-in-hole interactions between Fc heterodimers). A half antibody can be composed of one polypeptide chain or more than one polypeptide chains (e.g., the two polypeptide chains of a Fab). In an embodiment, a half-antibody comprises an Fc region.

An example of a half antibody is a molecule comprising a heavy and light chain of an antibody (e.g., an IgG antibody). Another example of a half antibody is a molecule comprising a first polypeptide comprising a VL domain and a CL domain, and a second polypeptide comprising a VH domain, a CH1 domain, a hinge domain, a CH2 domain, and a CH3 domain, where the VL and VH domains form an ABD. Yet another example of a half antibody is a polypeptide comprising an scFv domain, a CH2 domain and a CH3 domain.

A half antibody might include more than one ABD, for example a half-antibody comprising (in N- to C-terminal order) an scFv domain, a CH2 domain, a CH3 domain, and another scFv domain.

Half antibodies might also include an ABD chain that when associated with another ABD
5 chain in another half antibody forms a complete ABD.

Thus, a BBM can comprise one, more typically two, or even more than two half antibodies, and a half antibody can comprise one or more ABDs or ABD chains.

In some BBMs, a first half antibody will associate, *e.g.*, heterodimerize, with a second half antibody. In other BBMs, a first half antibody will be covalently linked to a second half
10 antibody, for example through disulfide bridges or chemical crosslinking. In yet other BBMs, a first half antibody will associate with a second half antibody through both covalent attachments and non-covalent interactions, for example disulfide bridges and knob-in-hole interactions.

The term "half antibody" is intended for descriptive purposes only and does not connote a particular configuration or method of production. Descriptions of a half antibody as a "first"
15 half antibody, a "second" half antibody, a "left" half antibody, a "right" half antibody or the like are merely for convenience and descriptive purposes.

Hole: In the context of a knob-into-hole, a "hole" refers to at least one amino acid side chain which is recessed from the interface of a first Fc chain and is therefore positionable in a compensatory "knob" on the adjacent interfacing surface of a second Fc chain so as to stabilize
20 the Fc heterodimer, and thereby favor Fc heterodimer formation over Fc homodimer formation, for example.

Host cell or recombinant host cell: The terms "host cell" or "recombinant host cell" refer to a cell that has been genetically-engineered, *e.g.*, through introduction of a heterologous nucleic acid. It should be understood that such terms are intended to refer not only to the
25 particular subject cell but to the progeny of such a cell. Because certain modifications can occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein. A host cell can carry the heterologous nucleic acid transiently, *e.g.*, on an extrachromosomal heterologous expression vector, or stably, *e.g.*, through integration of
30 the heterologous nucleic acid into the host cell genome. For purposes of expressing an antigen-binding molecule, a host cell can be a cell line of mammalian origin or mammalian-like characteristics, such as monkey kidney cells (COS, *e.g.*, COS-1, COS-7), HEK293, baby hamster kidney (BHK, *e.g.*, BHK21), Chinese hamster ovary (CHO), NSO, PerC6, BSC-1, human hepatocellular carcinoma cells (*e.g.*, Hep G2), SP2/0, HeLa, Madin-Darby bovine kidney
35 (MDBK), myeloma and lymphoma cells, or derivatives and/or engineered variants thereof. The

engineered variants include, e.g., glycan profile modified and/or site-specific integration site derivatives.

Humanized: The term “humanized” forms of non-human (e.g., murine) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin.

5 For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired specificity, affinity, and capacity. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding

10 non-human residues. Furthermore, humanized antibodies can comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or

15 substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally will also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Humanized antibodies are typically less immunogenic to humans, relative to non-humanized antibodies, and thus offer therapeutic benefits in certain situations. Humanized antibodies can be generated using known methods.

20 See for example, Hwang *et al.*, 2005, *Methods* 36:35; Queen *et al.*, 1989, *Proc. Natl. Acad. Sci. U.S.A.* 86:10029-10033; Jones *et al.*, 1986, *Nature* 321:522-25, 1986; Riechmann *et al.*, 1988, *Nature* 332:323-27; Verhoeyen *et al.*, 1988, *Science* 239:1534-36; Orlandi *et al.*, 1989, *Proc. Natl. Acad. Sci. U.S.A.* 86:3833-3837; U.S. Patent Nos. 5,225,539; 5,530,101; 5,585,089; 5,693,761; 5,693,762; and 6,180,370; and WO 90/07861. See also the following review articles

25 and references cited therein: Presta, 1992, *Curr. Op. Struct. Biol.* 2:593-596; Vaswani and Hamilton, 1998, *Ann. Allergy, Asthma & Immunol.* 1:105-115; Harris, 1995, *Biochem. Soc. Transactions* 23:1035-1038; Hurler and Gross, 1994, *Curr. Op. Biotech.* 5:428-433.

Human Antibody: The term “human antibody” as used herein includes antibodies having variable regions in which both the framework and CDR regions are derived from

30 sequences of human origin. Furthermore, if the antibody contains a constant region, the constant region also is derived from such human sequences, e.g., human germline sequences, or mutated versions of human germline sequences or antibody containing consensus framework sequences derived from human framework sequences analysis, for example, as described in Knappik *et al.*, 2000, *J Mol Biol* 296, 57-86. The structures and locations of

35 immunoglobulin variable domains, e.g., CDRs, can be defined using well known numbering schemes, e.g., the Kabat numbering scheme, the Chothia numbering scheme, or any combination of Kabat and Chothia (see, e.g., Lazikani *et al.*, 1997, *J. Mol. Bio.* 273:927-948;

Kabat *et al.*, 1991, Sequences of Proteins of Immunological Interest, 5th edit., NIH Publication no. 91-3242 U.S. Department of Health and Human Services; Chothia *et al.*, 1987, J. Mol. Biol. 196:901-917; Chothia *et al.*, 1989, Nature 342:877-883).

Human antibodies can include amino acid residues not encoded by human sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo, or a conservative substitution to promote stability or manufacturing). However, the term “human antibody”, as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

In combination: Administered “in combination,” as used herein, means that two (or more) different treatments are delivered to the subject during the course of the subject’s affliction with the disorder, e.g., the two or more treatments are delivered after the subject has been diagnosed with the disorder and before the disorder has been cured or eliminated or treatment has ceased for other reasons.

Knob: In the context of a knob-into-hole, a “knob” refers to at least one amino acid side chain which projects from the interface of a first Fc chain and is therefore positionable in a compensatory “hole” in the interface with a second Fc chain so as to stabilize the Fc heterodimer, and thereby favor Fc heterodimer formation over Fc homodimer formation, for example.

Knobs and holes (or knobs-into-holes): One mechanism for Fc heterodimerization is generally referred to in the art as “knobs and holes”, or “knob-in-holes”, or “knobs-into-holes”. These terms refer to amino acid mutations that create steric influences to favor formation of Fc heterodimers over Fc homodimers, as described in, e.g., Ridgway *et al.*, 1996, Protein Engineering 9(7):617; Atwell *et al.*, 1997, J. Mol. Biol. 270:26; and U.S. Patent No. 8,216,805. Knob-in-hole mutations can be combined with other strategies to improve heterodimerization.

Monoclonal Antibody: The term “monoclonal antibody” as used herein refers to polypeptides, including antibodies, antibody fragments, molecules (including BBMs), *etc.* that are derived from the same genetic source.

Monovalent: The term “monovalent” as used herein in the context of an antigen-binding molecule refers to an antigen-binding molecule that has a single antigen-binding domain.

Multispecific binding molecule: The term “multispecific binding molecule” or “MBM” refers to an antigen-binding molecule that specifically binds to at least two antigens and comprises two or more ABDs. The ABDs can each independently be an antibody fragment

(e.g., scFv, Fab, nanobody), a ligand, or a non-antibody derived binder (e.g., fibronectin, Fynomer, DARPin).

Mutation or modification: In the context of the primary amino acid sequence of a polypeptide, the terms “modification” and “mutation” refer to an amino acid substitution, insertion, and/or deletion in the polypeptide sequence relative to a reference polypeptide. Additionally, the term “modification” further encompasses an alteration to an amino acid residue, for example by chemical conjugation (e.g., of a drug or polyethylene glycol moiety) or post-translational modification (e.g., glycosylation).

Nucleic Acid: The term “nucleic acid” is used herein interchangeably with the term “polynucleotide” and refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. The term encompasses nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, and peptide-nucleic acids (PNAs).

Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, as detailed below, degenerate codon substitutions can be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzner *et al.*, (1991) *Nucleic Acid Res.* 19:5081; Ohtsuka *et al.*, (1985) *J. Biol. Chem.* 260:2605-2608; and Rossolini *et al.*, (1994) *Mol. Cell. Probes* 8:91-98).

Operably linked: The term “operably linked” refers to a functional relationship between two or more peptide or polypeptide domains or nucleic acid (e.g., DNA) segments. In the context of a fusion protein or other polypeptide, the term “operably linked” means that two or more amino acid segments are linked so as to produce a functional polypeptide. For example, in the context of an antigen-binding molecule, separate ABMs (or chains of an ABM) can be operably linked through peptide linker sequences. In the context of a nucleic acid encoding a fusion protein, such as a polypeptide chain of an antigen-binding molecule, “operably linked” means that the two nucleic acids are joined such that the amino acid sequences encoded by the two nucleic acids remain in-frame. In the context of transcriptional regulation, the term refers to the functional relationship of a transcriptional regulatory sequence to a transcribed sequence. For example, a promoter or enhancer sequence is operably linked to a coding

sequence if it stimulates or modulates the transcription of the coding sequence in an appropriate host cell or other expression system.

Polypeptide and Protein: The terms “polypeptide” and “protein” are used interchangeably herein to refer to a polymer of amino acid residues. The terms encompass amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. Additionally, the terms encompass amino acid polymers that are derivatized, for example, by synthetic derivatization of one or more side chains or termini, glycosylation, PEGylation, circular permutation, cyclization, linkers to other molecules, fusion to proteins or protein domains, and addition of peptide tags or labels.

Recognize: The term “recognize” as used herein refers to an ABD that finds and interacts (*e.g.*, binds) with its epitope.

Single Chain Fab or scFab: The terms “single chain Fab” and “scFab” mean a polypeptide comprising an antibody heavy chain variable domain (VH), an antibody constant domain 1 (CH1), an antibody light chain variable domain (VL), an antibody light chain constant domain (CL) and a linker, such that the VH and VL are in association with one another and the CH1 and CL are in association with one another. In some embodiments, the antibody domains and the linker have one of the following orders in N-terminal to C-terminal direction: a) VH-CH1-linker-VL-CL, b) VL-CL-linker-VH-CH1, c) VH-CL-linker-VL-CH1 or d) VL-CH1-linker-VH-CL. The linker can be a polypeptide of at least 30 amino acids, *e.g.*, between 32 and 50 amino acids. The single chain Fabs are stabilized via the natural disulfide bond between the CL domain and the CH1 domain.

Simultaneous or concurrent delivery: In some embodiments, the delivery of one treatment is still occurring when the delivery of a second begins, so that there is overlap in terms of administration. This is sometimes referred to herein as “simultaneous” or “concurrent delivery”. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, *e.g.*, an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

Single Chain Fv or scFv: By “single chain Fv” or “scFv” herein is meant a variable heavy domain covalently attached to a variable light domain, generally using an ABD linker as discussed herein, to form a scFv or scFv domain. A scFv domain can be in either orientation from N- to C-terminus (VH-linker-VL or VL-linker-VH). For a review of scFv see Plückthun in
 5 The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenberg and Moore eds., (1994) Springer-Verlag, New York, pp. 269-315.

Specifically (or selectively) binds: The term “specifically (or selectively) binds” to an antigen or an epitope refers to a binding reaction that is determinative of the presence of a cognate antigen or an epitope in a heterogeneous population of proteins and other biologics.
 10 An antigen-binding molecule or ABD of the disclosure typically has a dissociation rate constant (KD) (k_{off}/k_{on}) of less than $5 \times 10^{-2}M$, less than $10^{-2}M$, less than $5 \times 10^{-3}M$, less than $10^{-3}M$, less than $5 \times 10^{-4}M$, less than $10^{-4}M$, less than $5 \times 10^{-5}M$, less than $10^{-5}M$, less than $5 \times 10^{-6}M$, less than $10^{-6}M$, less than $5 \times 10^{-7}M$, less than $10^{-7}M$, less than $5 \times 10^{-8}M$, less than $10^{-8}M$, less than $5 \times 10^{-9}M$, or less than $10^{-9}M$, and binds to the target antigen with an affinity that is at least two-fold
 15 greater (and more typically at least 20-fold, at least 50-fold or at least 100-fold) than its affinity for binding to a non-specific antigen (e.g., HSA). Binding affinity can be measured using a Biacore, SPR or BLI assay.

The term “specifically binds” does not exclude cross-species reactivity. For example, an antigen-binding module (e.g., an antigen-binding fragment of an antibody) that “specifically
 20 binds” to an antigen from one species can also “specifically bind” to that antigen in one or more other species. Thus, such cross-species reactivity does not itself alter the classification of an antigen-binding module as a “specific” binder. In certain embodiments, an antigen-binding domain that specifically binds to a human antigen has cross-species reactivity with one or more non-human mammalian species, e.g., a primate species (including but not limited to one or
 25 more of *Macaca fascicularis*, *Macaca mulatta*, and *Macaca nemestrina*) or a rodent species, e.g., *Mus musculus*. In other embodiments, the antigen-binding domain does not have cross-species reactivity.

Subject: The term “subject” includes human and non-human animals. Non-human animals include all vertebrates, e.g., mammals and non-mammals, such as non-human
 30 primates, sheep, dog, cow, chickens, amphibians, and reptiles. Except when noted, the terms “patient” or “subject” are used herein interchangeably.

Tandem of VH Domains: The term “a tandem of VH domains (or VHs)” as used herein refers to a string of VH domains, consisting of multiple numbers of identical VH domains of an antibody. Each of the VH domains, except the last one at the end of the tandem, has its C-
 35 terminus connected to the N-terminus of another VH domain with or without a linker. A tandem has at least 2 VH domains, and in some embodiments a BBM has 3, 4, 5, 6, 7, 8, 9, or 10 VH

domains. The tandem of VH can be produced by joining the encoding nucleic acids of each VH domain in a desired order using recombinant methods with or without a linker that enables them to be made as a single polypeptide chain. The N-terminus of the first VH domain in the tandem is defined as the N-terminus of the tandem, while the C-terminus of the last VH domain in the tandem is defined as the C-terminus of the tandem.

Tandem of VL Domains: The term “a tandem of VL domains (or VLs)” as used herein refers to a string of VL domains, consisting of multiple numbers of identical VL domains of an antibody. Each of the VL domains, except the last one at the end of the tandem, has its C-terminus connected to the N-terminus of another VL with or without a linker. A tandem has at least 2 VL domains, and in some embodiments a BBM has 3, 4, 5, 6, 7, 8, 9, or 10 VL domains. The tandem of VL can be produced by joining the encoding nucleic acids of each VL domain in a desired order using recombinant methods with or without a linker that enables them to be made as a single polypeptide chain. The N-terminus of the first VL domain in the tandem is defined as the N-terminus of the tandem, while the C-terminus of the last VL domain in the tandem is defined as the C-terminus of the tandem.

Target Antigen: By “target antigen” as used herein is meant the molecule that is bound non-covalently, reversibly and specifically by an antigen binding domain.

Therapeutically effective amount: A “therapeutically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result.

Treat, Treatment, Treating: As used herein, the terms “treat”, “treatment” and “treating” refer to the reduction or amelioration of the progression, severity and/or duration of a proliferative disorder, or the amelioration of one or more symptoms (*e.g.*, one or more discernible symptoms) of a proliferative disorder resulting from the administration of one or more antigen-binding molecules. In some embodiments, the terms “treat”, “treatment” and “treating” refer to the amelioration of at least one measurable physical parameter of a proliferative disorder, such as growth of a tumor, not necessarily discernible by the patient. In other embodiments the terms “treat”, “treatment” and “treating” refer to the inhibition of the progression of a proliferative disorder, either physically by, *e.g.*, stabilization of a discernible symptom, physiologically by, *e.g.*, stabilization of a physical parameter, or both. In other embodiments the terms “treat”, “treatment” and “treating” refer to the reduction or stabilization of tumor size or cancerous cell count.

Tumor: The term “tumor” is used interchangeably with the term “cancer” herein, *e.g.*, both terms encompass solid and liquid, *e.g.*, diffuse or circulating, tumors. As used herein, the term “cancer” or “tumor” includes premalignant, as well as malignant cancers and tumors.

Variable region: By “variable region” or “variable domain” as used herein is meant the region of an immunoglobulin that comprises one or more Ig domains substantially encoded by any of the V κ , V λ , and/or V H genes that make up the kappa, lambda, and heavy chain immunoglobulin genetic loci respectively, and contains the CDRs that confer antigen specificity.

5 A “variable heavy domain” can pair with a “variable light domain” to form an antigen binding domain (“ABD”). In addition, each variable domain comprises three hypervariable regions (“complementary determining regions,” “CDRs”) (CDR-H1, CDR-H2, CDR-H3 for the variable heavy domain and CDR-L1, CDR-L2, CDR-L3 for the variable light domain) and four framework (FR) regions, arranged from amino-terminus to carboxy-terminus in the following order: FR1-
10 CDR1-FR2-CDR2-FR3-CDR3-FR4.

Vector: The term “vector” is intended to refer to a polynucleotide molecule capable of transporting another polynucleotide to which it has been linked. One type of vector is a “plasmid”, which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, where additional DNA
15 segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are
20 capable of directing the expression of genes to which they are operably linked. Such vectors are referred to herein as “recombinant expression vectors” (or simply, “expression vectors”). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, “plasmid” and “vector” can be used interchangeably as the plasmid is the most commonly used form of vector. However, the disclosure is intended to
25 include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

VH: The term “VH” refers to the variable region of an immunoglobulin heavy chain of an antibody, including the heavy chain of an Fv, scFv, dsFv or Fab.

VL: The term “VL” refers to the variable region of an immunoglobulin light chain,
30 including the light chain of an Fv, scFv, dsFv or Fab.

VH-VL or VH-VL Pair: In reference to a VH-VL pair, whether on the same polypeptide chain or on different polypeptide chains, the terms “VH-VL” and “VH-VL pair” are used for convenience and are not intended to convey any particular orientation, unless the context dictates otherwise. Thus, a scFv comprising a “VH-VL” or “VH-VL pair” can have the VH and
35 VL domains in any orientation, for example the VH N-terminal to the VL or the VL N-terminal to the VH.

7.2. BCMA Binding Molecules

The present disclosure provides therapeutic regimens and formulations of BCMA binding molecules. In some instances, the BCMA binding molecule can be any molecule (*e.g.*, chemical, protein, or nucleic acid) that binds to BCMA or can specifically target a BCMA
5 expressing molecule. For example, the BCMA binding molecule can be an antibody, chimeric antigen receptor T cell therapy (CAR-T), and/or a radioligand therapy (RLT).

Preferred BCMA binding molecules are multispecific binding molecules, *e.g.*, multispecific antibodies, more specifically bispecific binding molecules, *e.g.*, bispecific
10 antibodies, that bind to BCMA and CD3. In a particularly preferred embodiment, the BCMA binding molecule is the molecule referred to herein as BSBM3. BSBM3 has a Fab domain targeting BCMA and a single-chain Fv (scFv) domain targeting CD3. BSBM3 is composed of three polypeptides which, when expressed in the same cell, form two half antibodies as shown in FIG. 1. The first half antibody, composed of a heavy chain polypeptide having the amino
15 acid sequence of SEQ ID NO:1 associated with a light chain polypeptide having the amino acid sequence of SEQ ID NO:2, contains a Fab domain that binds to CD19. The second half antibody, composed of a heavy chain polypeptide having the amino acid sequence of SEQ ID NO:3, contains an scFv domain that binds to CD3. The Fc domain of BSBM3 contains substitutions that ablate binding to human Fcγ receptors in order to reduce the risk of non-
20 selective T cell activation via FcR (Fc receptor)-mediated crosslinking. Without being bound by theory, it is believed that the Fc domain confers IgG-like *in vivo* persistence due to unmodified FcRn (neonatal Fc receptor) affinity. It is also believed, without being bound by theory, that binding of multiple molecules of BSBM3 simultaneously with BCMA on multiple myeloma (MM) cells and the CD3 subunit of the T cell receptor (TCR) complex on T cells leads to TCR
25 crosslinking and formation of a cytolytic immune synapse, resulting in activation of T cells and specific lysis of MM cells.

7.3. Pharmaceutical Compositions

The BCMA binding molecules of the disclosure can be formulated as pharmaceutical compositions comprising the BCMA binding molecules, for example containing one or more
30 pharmaceutically acceptable excipients or carriers. To prepare pharmaceutical or sterile compositions comprising the BCMA binding molecules of the present disclosure a BCMA binding molecule preparation can be combined with one or more pharmaceutically acceptable excipient or carrier.

For example, formulations of BCMA binding molecules can be prepared by mixing
35 BCMA binding molecules with physiologically acceptable carriers, excipients, or stabilizers in the form of, *e.g.*, lyophilized powders, slurries, aqueous solutions, lotions, or suspensions (see,

e.g., Hardman *et al.*, 2001, Goodman and Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, N.Y.; Gennaro, 2000, Remington: The Science and Practice of Pharmacy, Lippincott, Williams, and Wilkins, New York, N.Y.; Avis *et al.* (eds.), 1993, Pharmaceutical Dosage Forms: General Medications, Marcel Dekker, NY; Lieberman *et al.* (eds.), 1990, Pharmaceutical Dosage Forms: Tablets, Marcel Dekker, NY; Lieberman *et al.* (eds.), 1990, Pharmaceutical Dosage Forms: Disperse Systems, Marcel Dekker, NY; Weiner and Kotkoskie, 2000, Excipient Toxicity and Safety, Marcel Dekker, Inc., New York, N.Y.).

For intravenous formulations, the BCMA binding molecule can be formulated with one or more excipients. In one embodiment, the BCMA binding molecule is formulated with an amino acid. In one embodiment, the BCMA binding molecule is formulated with a sugar. In one embodiment, the BCMA binding molecule is formulated with a surfactant. In one embodiment, the BCMA binding molecule is formulated with water. In some embodiments, the BCMA binding molecule can be formulated with one or more of an amino acid, a sugar, or a surfactant.

In some embodiments, the amino acid can be histidine. In some embodiments, the sugar can be sucrose. In some embodiments, the surfactant can be polysorbate, such as polysorbate 20 ("PS20"), also known as Tween 20.

Accordingly, the disclosure provides pharmaceutical compositions comprising a BCMA binding molecule and (a) an amino acid such as histidine; (b) a sugar such as sucrose; (c) a surfactant such as PS20 ; or (d) a combination of any two or all of the foregoing. For parenteral, e.g., intravenous, administration, the pharmaceutical composition can be a liquid pharmaceutical composition.

Suitable concentrations of histidine range from 10 mM to 50 mM. In an embodiment, the concentration of histidine is 20 mM.

Suitable concentrations of sucrose range from 150 mM to 300 mM. In an embodiment, the concentration of sucrose is 240 mM.

Suitable concentrations of PS20 range from 0.02% to 0.06%. In an embodiment, the concentration of PS20 is 0.04%.

The pharmaceutical composition can be lyophilized and reconstituted in a suitable volume of liquid to obtain a solution for administration containing one or more of histidine, sucrose and PS20, e.g., in the concentrations described above.

In some embodiments, the pH of the formulation can be acidic. For example, in one embodiment, the pH of the formulation can be about 5.0 to about 6.5. In one embodiment, the pH of the formation can be about 5.0 to about 6.0. In some embodiment, the pH of the formulation can be about 5.5.

A suitable pH range for a liquid pharmaceutical composition comprising a BCMA binding molecule for parenteral, e.g., intravenous, administration is acidic, e.g., about 5.0 to about 6.5. In certain aspects, the pH is about 5.0 to about 6.0 and in some embodiments the pH is about 5.5.

5 A suitable concentration range for the BCMA binding molecule is between 5 mg/mL and 20 mg/mL, and in an embodiment is 10 mg/mL.

Accordingly, in a particular embodiment, the disclosure provides a vial comprising (a) 10 mg/mL of BSBM3; (b) 20mM histidine; (c) 240 mM sucrose; (d) 0.04% PS20; and (e) a pH of about 5.5±0.3.

10 The GSi of the disclosure can be formulated in a variety of manners. For example, in some instances, the GSi can be formulated so as to be administered orally. In some embodiments, the GSi can be formulated as liquid. In other embodiments, the GSi can be formulated into a capsule.

8. DOSING

15 8.1. BCMA Binding Molecule

8.1.1. Amount of BCMA Binding Molecule

BCMA binding molecules can be used for the prevention and/or treatment of cancer. In some embodiments, the subject has been previously treated with one prior treatment regimens that does not comprise a BCMA binding molecule. In some embodiments, the subject has
20 been previously treated with two prior treatments regimens that do not comprise a BCMA binding molecule. In some embodiments, the subject has been previously treated with three or more prior treatment regimens that do not comprise a BCMA binding molecule.

In some embodiments, the subject can be dosed with the BCMA binding molecule with about 0.5 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding
25 molecule with about 1 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule with about 10 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule with about 30 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule with about 50 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule with about 75 µg/kg. In some
30 embodiments, the subject can be dosed with the BCMA binding molecule with about 100 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule with about 200 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule with about 300 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule with about 400 µg/kg. In some embodiments, the subject can be dosed with the
35 BCMA binding molecule with about 500 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule with about 600 µg/kg. In some embodiments, the

subject can be dosed with the BCMA binding molecule with about 700 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule with about 800 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule with about 900 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule with about 1000 µg/kg.

In some embodiments, the subject can be dosed with the BCMA binding molecule at a dose of at least 1 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule at a dose of at least 5 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule at a dose of at least 10 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule at a dose of at least 12 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule at a dose of at least 15 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule at a dose of at least 20 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule at a dose of at least 25 µg/kg. In some embodiments, the subject can be dosed with the BCMA binding molecule at a dose of at least 30 µg/kg.

In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 1 µg/kg to about 20 µg/kg. In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 20 µg/kg to about 40 µg/kg. In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 80 µg/kg to about 120 µg/kg. In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 150 µg/kg to about 250 µg/kg. In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 300 µg/kg to about 500 µg/kg. In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 500 µg/kg to about 700 µg/kg. In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 600 µg/kg to about 900 µg/kg.

In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 0.25 µg/kg to about 1200 µg/kg, for example, in some embodiments, the subject can be dosed with the BCMA binding molecule with about 1 µg/kg to about 1000 µg/kg. In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 10 µg/kg to about 900 µg/kg. In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 20 µg/kg to about 800 µg/kg. In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 30 µg/kg to about 700 µg/kg. In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 50 µg/kg to about 600 µg/kg. In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 75 µg/kg to about 500 µg/kg. In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 100 µg/kg to about 400 µg/kg. In some

embodiments, the subject can be administered the BCMA binding molecule at a dose of about 150 µg/kg to about 300 µg/kg. In some embodiments, the subject can be administered the BCMA binding molecule at a dose of about 200 µg/kg to about 250 µg/kg.

In some embodiments, the subject can be dosed with the BCMA binding molecule at a
5 dose of about 0.5 µg/kg to about 20 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 0.5 µg/kg to 10 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 1 µg/kg to 10 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 5 µg/kg to 10 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of
10 the subject at a dose of about 1 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 3 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 6 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 10 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 10
15 µg/kg to 20 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 10 µg/kg to 15 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 12 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 20 µg/kg to about 40 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose
20 of about 20 µg/kg to about 30 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 24 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 30 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 40 µg/kg to about 80 µg/kg. In one embodiment, the BCMA binding molecule is administered to the
25 subject at a dose of about 40 µg/kg to about 60 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 48 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 80 µg/kg to about 120 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 80 µg/kg to about 100 µg/kg. In one embodiment, the BCMA binding molecule is
30 administered to the subject at a dose of about 96 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 100 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 100 µg/kg to about 200 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 150 µg/kg to about 200 µg/kg. In one embodiment, the BCMA binding molecule is
35 administered to the subject at a dose of about 192 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 150 µg/kg to about 250 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a

dose of about 200 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 300 µg/kg to about 500 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 384 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 400 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 500 µg/kg to about 700 µg/kg. In one embodiment, the BCMA binding molecule is administered to the subject at a dose of about 600 µg/kg.

Further, any of the dosing amounts disclosed throughout this disclosure can be used to dose the BCMA binding molecule, *e.g.*, as a first or subsequent treatment dose.

In an embodiment, a treatment dose can be about 1 µg/kg to about 1200 µg/kg or about 50 µg to about 96 mg. In another embodiment, a treatment dose can be about 3 µg/kg to about 600 µg/kg or about 150 µg to about 48 mg. In another embodiment, a treatment dose can be about 5 µg/kg to about 100 µg/kg or about 150 µg to about 8 mg. In another embodiment, a treatment dose can be about 10 µg/kg to about 200 µg/kg or about 500 µg to about 16 mg. In another embodiment, a treatment dose can be about 50 µg/kg to about 400 µg/kg or about 2.5 mg to about 32 mg. In another embodiment, a treatment dose can be about 100 µg/kg to about 600 µg/kg or about 5 mg to about 96 mg. In another embodiment, a treatment dose can be about 1 µg/kg or about 50 µg to about 80 µg. In another embodiment, a treatment dose can be about 3 µg/kg. In another embodiment, a treatment dose can be about 150 µg to about 240 µg. In another embodiment, a treatment dose can be about 6 µg/kg or about 300 µg to about 480 µg. In another embodiment, a treatment dose can be about 12 µg/kg or about 600 µg to about 960 µg. In another embodiment, a treatment dose can be about 24 µg/kg or about 1.2 mg to about 1.92 mg. In another embodiment, a treatment dose can be about 48 µg/kg or about 2.4 mg to about 3.84 mg. In another embodiment, a treatment dose can be about 96 µg/kg or about 4.8 mg to about 7.68 mg. In another embodiment, a treatment dose can be about 192 µg/kg or about 9.6 mg to about 15.36 mg. In another embodiment, a treatment dose can be about 384 µg/kg or about 19.2 mg to about 30.72 mg. In another embodiment, a treatment dose can be about 600 µg/kg or about 30 mg to about 48 mg.

In some instances, a priming dose is needed or used. The priming dose can be any of the doses described herein, and in some embodiments is lower than the first treatment dose. For example, if the first treatment dosing amount of the BCMA binding molecule is 30 µg/kg, the priming dose can be administered at any dose lower than 30 µg/kg. In this particular case, the priming dose can be administered at a dose lower than 30 µg/kg, for example lower than 29 µg/kg, *e.g.*, 10 µg/kg or 1 µg/kg.

In some embodiments, the priming dose is initiated one week prior to administering the first BCMA binding molecule dose. In other embodiments, a priming dose is equal to the first treatment dose. A priming dose can be administered in a single administration or, alternatively,

administered over multiple administrations (e.g., two). In some embodiments, the priming dose is divided. In some embodiments, the priming dose is administered over a period of two days. In some embodiments, one third of a priming dose is administered on a first day, and two thirds of the priming dose is administered on a second day, for example the day after the first day. In some embodiments, less than half the priming dose is administered on the first day and the remainder of the priming dose is administered on the second day. In some embodiments, about a third of the priming dose is administered on the first day and about two thirds of the priming dose is administered on the second day.

In an embodiment, the priming dose ranges about 0.5 µg/kg to about 6 µg/kg or about 25 µg to about 480 µg. In another embodiment, the priming dose is about 1 µg/kg or about 50 µg to about 80 µg. In another embodiment, the priming dose is about 2 µg/kg or about 100 µg to about 160 µg. In another embodiment, the priming dose is about 3 µg/kg or about 150 µg to about 240 µg. In another embodiment, the priming dose is about 4 µg/kg or about 200 µg to about 320 µg. In another embodiment, the priming dose is about 5 µg/kg or about 250 µg to about 400 µg. In another embodiment, the priming dose is about 6 µg/kg or about 300 µg to about 480 µg.

8.1.2. Dosing time of BCMA binding molecule

The BCMA binding molecule can be administered to the subject in any effective way. The dose can be administered over a number hours. For example, if the BCMA binding molecule is administered intravenously, it can be done via infusion. The infusion can occur over a span over about 30 minutes to about 6 hours. In some embodiments, the infusion can occur over a span of about 30 minutes. In some embodiments, the infusion can occur over a span of about 1 hour. In some embodiments, the infusion can occur over a span of about 1.5 hours. In some embodiments, the infusion can occur over a span of about 2 hours. In some embodiments, the infusion can occur over a span of about 2.5 hours. In some embodiments, the infusion can occur over a span of about 3 hours. In some embodiments, the infusion can occur over a span of about 3.5 hours. In some embodiments, the infusion can occur over a span of about 4 hours. In some embodiments, the infusion can occur over a span of about 4.5 hours. In some embodiments, the infusion can occur over a span of about 5 hours. In some embodiments, the infusion can occur over a span of about 5.5 hours. In some embodiments, the infusion can occur over a span of about 6 hours.

In some embodiments, the infusion can occur over a span of about 30 minutes to about 1 hour. In some embodiments, the infusion can occur over a span of about 1 hour to about 2 hours. In some embodiments, the infusion can occur over a span of about 2 hours to about 3 hours. In some embodiments, the infusion can occur over a span of about 3 hours to about 4 hours. In some embodiments, the infusion can occur over a span of about 4 hours to about 5 hours. In some embodiments, the infusion can occur over a span of about 5 hours to about 6

hours. In some embodiments, the infusion can occur over a span of about 30 minutes to about 6 hours. In some embodiments, the infusion can occur over a span of about 1 hour to about 5 hours. In some embodiments, the infusion can occur over a span of about 1.5 hours to about 4 hours. In some embodiments, the infusion can occur over a span of about 2 hours to about 3 hours.

Further, any of the dosing time disclosed throughout can be used to dose the BCMA binding molecule and/or any of the other therapeutic agents disclosed throughout.

8.1.3. Dosing Schedule of BCMA binding molecule

In some embodiments, the BCMA binding molecule can be dosed once a week per dosing cycle. In some embodiments, the BCMA binding molecule can be dosed twice a week per dosing cycle. In some embodiments, the BCMA binding molecule can be dosed once every two weeks per dosing cycle.

In some embodiments, the BCMA binding molecule can be dosed a single time per dosing cycle. In some embodiments, the BCMA molecule can be dosed twice per dosing cycle. In some embodiments, the BCMA binding molecule can be dosed three times per dosing cycle. In some embodiments, the BCMA binding molecule can be dosed four times per dosing cycle.

In a dosing cycle, the BCMA binding molecule can be dosed for 1 week. In some embodiments, the BCMA binding molecule can be dosed for 2 weeks in a dosing cycle. In some embodiments, the BCMA binding molecule can be dosed for 3 weeks in a dosing cycle. In some embodiments, the BCMA binding molecule can be dosed for 4 weeks in a dosing cycle.

The BCMA binding molecule can also be administered to the subject one or more times over the course of time. For example, in one embodiment, the BCMA binding molecule can be administered to the subject, once a week for four weeks.

In some embodiments, the BCMA binding molecule can be dosed until remission (with regards to cancers), *e.g.*, until a response is observed. In some embodiments, the BCMA binding molecule can be dosed until partial remission, *e.g.*, until a partial response is observed. In some embodiments, the BCMA binding molecule can be dosed until complete remission, *e.g.*, until a complete response is observed. In some embodiments, the administering of the BCMA binding molecule continues until the subject experiences toxicity. In some embodiments, the administering of the BCMA binding molecule continues until a physician determines that the subject should no longer be dosed with the BCMA binding molecule.

With regards to any priming doses given, the priming dose of the BCMA binding molecule can be administered prior to a first treatment dose at any time before the treatment dose is given. For example, the priming dose can be administered once a week before the first treatment dose is given. In another example, the priming dose can be administered twice within one week before the first treatment dose is given.

In some embodiments, one third of a priming dose is administered to the subject on day 1 of a course of treatment, with the remainder of the priming dose administered on day 2 of the treatment. In some embodiments, a first treatment dose is subsequently administered to the subject one of days 5-11 of the treatment (*e.g.*, one of days 6-10, one of days 7-9 or day 8), a second treatment dose is subsequently administered to the subject one of days 12-18 of the treatment (*e.g.*, one of days 13-17, one of days 14-16, or day 15), and a third treatment dose is subsequently administered to the subject one of days 19-25 (*e.g.*, one of days 20-24, one of days 21-23, or day 22) of the treatment.

8.2. Gamma Secretase Inhibitor (GSI)

8.2.1. GSI and GSI Amount

GSI can be used for the prevention and/or treatment of cancer (*e.g.*, a blood cancer such as multiple myeloma). In some embodiments, the GSI can be used to enhance the effect of a therapeutic agent. In some embodiments, the GSI can be used alone.

The GSI doses can be administered in various forms, such as those suitable for oral dosing, such as in capsule form and liquid form.

In some embodiments, the GSI is LY-450139, PF-5212362, BMS-708163, MK-0752, ELN-318463, BMS-299897, LY-411575, DAPT, AL-101 (BMS-906024), AL-102 (BMS-986115), PF-3084014, RO4929097, LY3039478, or any combination thereof. For example, in some embodiments, the preferred GSI is AL-102 also known as BMS-986115.

In some embodiments, the GSI is administered at a dose of about 0.1 mg to about 10 mg. In some embodiments, the GSI is administered at a dose of about 0.5 mg to about 9 mg. In some embodiments, the GSI is administered at a dose of about 0.75 mg to about 8 mg. In some embodiments, the GSI is administered at a dose of about 0.9 mg to about 7 mg. In some embodiments, the GSI is administered at a dose of about 1 mg to about 6 mg. In some embodiments, the GSI is administered at a dose of about 2 mg to about 5 mg. In some embodiments, the GSI is administered at a dose of about 3 mg to about 4 mg. In some embodiments, the GSI is administered at a dose of about 0.75 mg to about 5 mg. In some embodiments, the GSI is administered at a dose of about 0.8 mg to about 4 mg. In some embodiments, the GSI is administered at a dose of about 0.9 mg to about 3 mg.

In some embodiments, the GSI is administered at a dose of about 0.9 mg. In some embodiments, the GSI is administered at a dose of about 1 mg. In some embodiments, the GSI is administered at a dose of about 2 mg. In some embodiments, the GSI is administered at a dose of about 3 mg. In some embodiments, the GSI is administered at a dose of about 4 mg. In some embodiments, the GSI is administered at a dose of about 5 mg. In some embodiments, the GSI is administered at a dose of about 6 mg. In some embodiments, the GSI is administered at a dose of about 7 mg. In some embodiments, the GSI is administered at a

dose of about 8 mg. In some embodiments, the GSi is administered at a dose of about 9 mg. In some embodiments, the GSi is administered at a dose of about 10 mg.

8.2.2. Dosing time of GSi

In some embodiments, the GSi is administered to the subject via an oral route, such as in the form of a capsule or liquid. The single dosage can be however divided up into several doses. For example, 2 or more capsules can be given to the subject over the course of a single administration. For example, 1 capsule can be administered to the subject and then in a specified time later (*e.g.*, 10 seconds, 30 seconds, 1 minutes, 5 minutes) an additional capsule can be administered to the subject.

8.2.3. Dosing Schedule of GSi

In some embodiments, the GSi is administered twice a week, as a first GSi dose and a second GSi dose. In some embodiments, the first GSi dose and the second GSi dose are administered on two consecutive days. In some embodiments, the first GSi dose and the second GSi dose are administered on the same day. In some embodiments, the first GSi dose and the second GSi dose are administered on two non-consecutive days. In some embodiments, the first GSi dose is administered about 24 hours prior the second GSi dose. In some embodiments, after the second GSi dose is administered to the subject, the GSi is not readministered for at least 5 consecutive days.

When combinations are used, for example, in the context of a BCMA binding molecule such as a BCMAxCD3 bispecific antibody or a BCMA specific CAR-T, a GSi can be administered before any such BCMA binding molecule is administered. In some embodiments, the GSi can be administered only before the BCMA molecule is administered. In some embodiments, the GSi can be administered only concurrently with BCMA molecule. In some embodiments, the GSi can be administered only after the BCMA molecule is administered. In some embodiments, more than one dose of the GSi can be administered in any given dosing cycle.

Two or more doses of GSi and one or more dose of a BCMA binding molecule can be administered in any given dosing cycle. In some embodiments, the first GSi dose is administered to the subject one day before the BCMA binding molecule is administered. In some embodiments, the second GSi dose is administered to the subject on the same day as the BCMA binding molecule. In some embodiments, the first GSi dose is administered to the subject the day before the BCMA binding molecule is administered and the second GSi dose is administered to the subject on the next day along with the BCMA binding molecule. In some embodiments, the second GSi dose is administered to the subject about 2 hours prior to the administration of the BCMA binding molecule.

8.3. Side Effect Reducing Agents

With regards to side effect reducing agents, the agents and doses as described throughout the disclosure can be used in the manner as described throughout the disclosure. Further, these side effect reducing agents can be used as they are known to be safe and effective. Specific side effect reducing agents are disclosed throughout but can also include and are not limited to paracetamol, acetaminophen, antihistamines (e.g., diphenhydramine), steroids (e.g., glucocorticoids, e.g., prednisone, cortisone, dexamethasone), anti-T cell directed therapy (e.g., tocilizumab or canakinumab), antidiarrheals (e.g., loperamide), octreotide, emollients, antibiotics, or any combination thereof.

9. COMBINATIONS

9.1. BCMA + GSi Combinations

The BCMA binding molecule can be used in combination with a gamma secretase inhibitor ("GSi"). The term "GSi" includes a gamma secretase inhibitor, which can be in any form. In some embodiments, the GSi is a small molecule (e.g., a chemical) or is a large molecule (e.g., a protein). The term "GSi" also encompasses a metabolite (e.g., an active metabolite) thereof.

Accordingly, in one aspect, the disclosure provides a method for treating subjects that have a disease associated with expression of BCMA, comprising administering to the subject an effective amount of: (i) a BCMA binding molecule, and (ii) a gamma secretase inhibitor (GSi).

In another aspect, the disclosure provides a method for treating subjects that have undergone treatment for a disease associated with expression of BCMA, comprising administering to the subject an effective amount of: (i) a BCMA binding molecule, and (ii) a GSi.

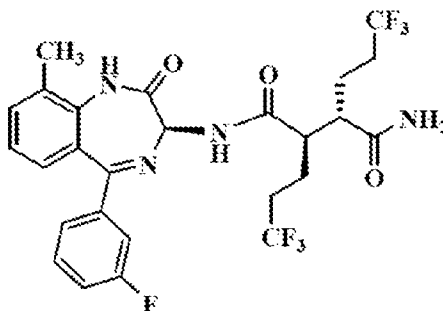
The BCMA binding molecule and GSi combination as disclosed can be used for treatment or prevention of cancer. In some embodiments, the BCMA binding molecule and GSi combination can be used for the manufacture of a medicament for treating or preventing cancer.

In one embodiment, the BCMA binding molecule and the GSi are administered simultaneously or sequentially. In one embodiment, the BCMA binding molecule is administered prior to the administration of the GSi. In one embodiment, the GSi is administered prior to the administration of the BCMA binding molecule. In one embodiment, the BCMA binding molecule and the GSi are administered simultaneously.

In one embodiment, the GSi is administered prior to the administration of the BCMA binding molecule (e.g., GSi is administered 1, 2, 3, 4, or 5 days prior to the administration of the BCMA binding molecule), optionally where after the administration of the GSi and prior to the

administration of the BCMA binding molecule, the subject shows an increase in cell surface BCMA expression levels and/or a decrease in soluble BCMA levels.

In some embodiments, the GSI is AL-102. The structure of AL-102 is shown below:



5 In some embodiments, the GSi is a metabolite of AL-102. In some embodiments, the metabolite of GSi is an active metabolite. In other embodiments, the active metabolite also functions as a gamma secretase inhibitor. In these cases, the active metabolite is not toxic.

The BCMA binding molecules and the GSis disclosed throughout can be administered to a subject in need thereof (e.g., those having a blood cancer). For example, disclosed herein is
 10 a method of treating a subject suffering from cancer (e.g., multiple myeloma) comprising administering to the subject one or more treatment doses of a B-cell maturation antigen (BCMA) binding molecule and a gamma secretase inhibitor (GSI).

The dosing and timing of administration of the BCMA binding molecule and the GSi can differ. For example, in the context of a BCMA binding molecule such as a BCMAxCD3
 15 bispecific antibody or a BCMA specific CAR-T, a GSi can be administered before any such BCMA binding molecule is administered. In some embodiments, the GSi can be administered only before the BCMA molecule is administered. In some embodiments, the GSi can be administered only concurrently with BCMA molecule. In some embodiments, the GSi can be administered only after the BCMA molecule is administered. In some embodiments, the GSi
 20 can be administered in more than one doses in any given dosing cycle.

In some embodiments, the first GSi dose is administered to the subject one day before the BCMA binding molecule is administered. In some embodiments, the second GSi dose is administered to the subject on the same day as the BCMA binding molecule. In some
 25 embodiments, the first GSi dose is administered to the subject the day before the BCMA binding molecule is administered and the second GSi dose is administered to the subject on the next day along with the BCMA binding molecule. In some embodiments, the second GSi dose is administered to the subject about 2 hours prior to the administration of the BCMA binding molecule.

In some embodiments, a BCMA binding molecule (e.g., a BCMA bispecific antibody) is
 30 administered to the subject at a dose of about 6 µg/kg and a first and/or second GSi dose is

administered to the subject at a dose of about 0.9 mg. In some embodiments, a BCMA binding molecule (e.g., a BCMA bispecific antibody) is administered to the subject at a dose of about 12 µg/kg and a first and/or second GSi dose is administered to the subject at a dose of about 0.9 mg. In some embodiments, a BCMA binding molecule (e.g., a BCMA bispecific antibody) is administered to the subject at a dose of about 12 µg/kg and a first and/or second GSi dose is administered to the subject at a dose of about 2 mg. In some embodiments, a BCMA binding molecule (e.g., a BCMA bispecific antibody) is administered to the subject at a dose of about 24 µg/kg and a first and/or second GSi dose is administered to the subject at a dose of about 2 mg. In some embodiments, a BCMA binding molecule (e.g., a BCMA bispecific antibody) is administered to the subject at a dose of about 48 µg/kg and a first and/or second GSi dose is administered to the subject at a dose of about 2 mg. In some embodiments, a BCMA binding molecule (e.g., a BCMA bispecific antibody) is administered to the subject at a dose of about 48 µg/kg and a first and/or second GSi dose is administered to the subject at a dose of about 4 mg. In some embodiments, a BCMA binding molecule (e.g., a BCMA bispecific antibody) is administered to the subject at a dose of about 96 µg/kg and a first and/or second GSi dose is administered to the subject at a dose of about 4 mg. In some embodiments, a BCMA binding molecule (e.g., a BCMA bispecific antibody) is administered to the subject at a dose of about 192 µg/kg and a first and/or second GSi dose is administered to the subject at a dose of about 4 mg. In some embodiments, a BCMA binding molecule (e.g., a BCMA bispecific antibody) is administered to the subject at a dose of about 384 µg/kg and a first and/or second GSi dose is administered to the subject at a dose of about 4 mg. In some embodiments, a BCMA binding molecule (e.g., a BCMA bispecific antibody) is administered to the subject at a dose of about 384 µg/kg and a first and/or second GSi dose is administered to the subject at a dose of about 6 mg.

Each of the above BCMA binding molecule + GSi dosage regimens can be considered one cycle. In some embodiments, each cycle can continue until treatment is discontinued. For example, discontinuation of treatment can occur when the patient no longer responds to treatment, the negative side effects outweigh the benefit of treatment, the patient dies, the patient has a complete response, the patient has a partial response, the patient has stable disease, or any combination thereof.

The above mentioned dosing cycles can continue for 1 to 100 cycles. For example, in some embodiments, the number of dosing cycles can be 2 cycles. In some embodiments, the number of dosing cycles can be 3 cycles. In some embodiments, the number of dosing cycles can be 4 cycles. In some embodiments, the number of dosing cycles can be 5 cycles. In some embodiments, the number of dosing cycles can be 6 cycles. In some embodiments, the number of dosing cycles can be 7 cycles. In some embodiments, the number of dosing cycles can be 8 cycles. In some embodiments, the number of dosing cycles can be 9 cycles. In some

embodiments, the number of dosing cycles can be 10 cycles. In some embodiments, the number of dosing cycles can be 11 cycles. In some embodiments, the number of dosing cycles can be 12 cycles. In some embodiments, the number of dosing cycles can be 13 cycles. In some embodiments, the number of dosing cycles can be 14 cycles. In some embodiments, the number of dosing cycles can be 15 cycles. In some embodiments, the number of dosing cycles can be at least 16 cycles. In some embodiments, the number of dosing cycles can be at least 20 cycles. In some embodiments, the number of dosing cycles can be at least 25 cycles. In some embodiments, the number of dosing cycles can be at least 30 cycles. In some embodiments, the number of dosing cycles can be at least 35 cycles. In some embodiments, the number of dosing cycles can be at least 40 cycles. In some embodiments, the number of dosing cycles can be at least 45 cycles. In some embodiments, the number of dosing cycles can be at least 50 cycles. In some embodiments, the number of dosing cycles can be at least 52 cycles.

In one aspect, the disclosure provides a method for treating subjects having a B cell condition or disorder, comprising administering to the subject an effective amount of: (i) a BCMA binding molecule, and (ii) a gamma secretase modulator (e.g., a GSI). Exemplary B cell conditions or disorders that can be treated with the combination of a BCMA binding molecule and a gamma secretase modulator include multiple myeloma, Waldenstrom's macroglobulinemia, chronic lymphocytic leukemia, B cell non-Hodgkin's lymphoma, plasmacytoma, Hodgkins' lymphoma, follicular lymphomas, small non-cleaved cell lymphomas, endemic Burkitt's lymphoma, sporadic Burkitt's lymphoma, marginal zone lymphoma, extranodal mucosa-associated lymphoid tissue lymphoma, nodal monocytoid B cell lymphoma, splenic lymphoma, mantle cell lymphoma, large cell lymphoma, diffuse mixed cell lymphoma, immunoblastic lymphoma, primary mediastinal B cell lymphoma, pulmonary B cell angiocentric lymphoma, small lymphocytic lymphoma, B cell proliferations of uncertain malignant potential, lymphomatoid granulomatosis, post-transplant lymphoproliferative disorder, an immunoregulatory disorder, rheumatoid arthritis, myasthenia gravis, idiopathic thrombocytopenia purpura, anti-phospholipid syndrome, Chagas' disease, Grave's disease, Wegener's granulomatosis, poly-arteritis nodosa, Sjogren's syndrome, pemphigus vulgaris, scleroderma, multiple sclerosis, anti-phospholipid syndrome, ANCA associated vasculitis, Goodpasture's disease, Kawasaki disease, autoimmune hemolytic anemia, rapidly progressive glomerulonephritis, heavy-chain disease, primary or immunocyte-associated amyloidosis, or monoclonal gammopathy of undetermined significance.

9.2. Additional Combinations

A BCMA binding molecule and/or the GSI of the disclosure can be used in combination other known agents and therapies.

For example, the BCMA binding molecules and/or the GSi can be used in treatment regimens in combination with surgery, chemotherapy, antibodies, radiation, peptide vaccines, steroids, cytotoxins, proteasome inhibitors, immunomodulatory drugs (e.g., IMiDs), BH3 mimetics, cytokine therapies, stem cell transplant or any combination thereof.

5 For convenience, an agent that is used in combination with a BCMA binding molecule and/or GSi is referred to herein as an “additional” agent.

Administered “in combination,” as used herein, means that two (or more) different treatments are delivered to the subject during the course of the subject’s affliction with the disorder, e.g., the two or more treatments are delivered after the subject has been diagnosed
10 with the disorder and before the disorder has been cured or eliminated or treatment has ceased for other reasons. In some embodiments, the delivery of one treatment is still occurring when the delivery of the second begins, so that there is overlap in terms of administration. This is sometimes referred to herein as “simultaneous” or “concurrent delivery”. The term “concurrently” is not limited to the administration of therapies (e.g., a BCMA binding molecule
15 and/or GSi and an additional agent) at exactly the same time, but rather it is meant that a pharmaceutical composition comprising a BCMA binding molecule and/or GSi is administered to a subject in a sequence and within a time interval such that the BCMA binding molecules and/or GSi can act together with the additional therapy(ies) to provide an increased benefit than if they were administered otherwise. For example, each therapy can be administered to a
20 subject at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic effect.

A BCMA binding molecule and/or GSi and one or more additional agents can be administered simultaneously, in the same or in separate compositions, or sequentially. For
25 sequential administration, the BCMA binding molecule and/or GSi can be administered first, and the additional agent can be administered second, or the order of administration can be reversed.

The BCMA binding molecule and/or GSi and the additional agent(s) can be administered to a subject in any appropriate form and by any suitable route. In some
30 embodiments, the routes of administration are the same. In other embodiments the routes of administration are different.

In other embodiments, the delivery of one treatment ends before the delivery of the other treatment begins.

In some embodiments of either case, the treatment is more effective because of
35 combined administration. For example, the additional treatment is more effective, e.g., an equivalent effect is seen with less of the additional treatment, or the additional treatment

reduces symptoms to a greater extent, than would be seen if the additional treatment were administered in the absence of the BCMA binding molecule and/or GSi treatment, or the analogous situation is seen with the BCMA binding molecule and/or GSi treatment. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the combined treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the BCMA binding molecule and/or GSi treatment delivered is still detectable when the additional treatment is delivered.

The BCMA binding molecule and/or GSi and/or additional agents can be administered during periods of active disorder, or during a period of remission or less active disease. A BCMA binding molecule and/or GSi can be administered before the treatment with the additional agent(s), concurrently with the treatment with the additional agent(s), post-treatment with the additional agent(s), or during remission of the disorder.

When administered in combination, the BCMA binding molecule and/or GSi and/or the additional agent(s) can be administered in an amount or dose that is higher, lower or the same than the amount or dosage of each agent used individually, e.g., as a monotherapy. For example, in some embodiments, the BCMA binding molecule when used in combination can be administered in an amount or dose that is lower than would be used as a monotherapy.

The additional agent(s) of the combination therapies of the disclosure can be administered to a subject concurrently. The term "concurrently" is not limited to the administration of therapies (e.g., prophylactic or therapeutic agents) at exactly the same time, but rather it is meant that a pharmaceutical composition comprising a BCMA binding molecule and/or GSi is administered to a subject in a sequence and within a time interval such that the molecules of the disclosure can act together with the additional therapy(ies) to provide an increased benefit than if they were administered otherwise. For example, each therapy can be administered to a subject at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. Each therapy can be administered to a subject separately, in any appropriate form and by any suitable route.

The BCMA binding molecule and/or GSi and the additional agent(s) can be administered to a subject by the same or different routes of administration.

The BCMA binding molecules and/or GSi and the additional agent(s) can be cyclically administered. Cycling therapy involves the administration of a first therapy (e.g., a first prophylactic or therapeutic agent) for a period of time, followed by the administration of a second therapy (e.g., a second prophylactic or therapeutic agent) for a period of time,

optionally, followed by the administration of a third therapy (e.g., prophylactic or therapeutic agent) for a period of time and so forth, and repeating this sequential administration, *i.e.*, the cycle in order to reduce the development of resistance to one of the therapies, to avoid or reduce the side effects of one of the therapies (e.g., the BCMA binding molecule and/or GSi), and/or to improve the efficacy of the therapies. In some embodiments, the one or more additional therapeutic agents reduces a side effect of the GSi and/or the BCMA binding molecule. In some embodiments, the side effect is cytokine release syndrome (CRS).

In certain instances, the one or more additional therapeutic agents, are other anti-cancer agents, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, and combinations thereof. In some embodiments, the additional therapeutic agents can be antidiarrheals (e.g., loperamide), octreotide, glucocorticoids (e.g, prednisone, cortisone, dexamethasone), emollients, antibiotics, paracetamol, acetaminophen, antihistamines, anti-T cell directed therapy, or any combination thereof.

In some embodiments, the additional therapeutic agent is a glucocorticoid. For example, the glucocorticoid can be dexamethasone or methylprednisolone. In some embodiments, glucocorticoid is dexamethasone and is administered at a dose of about 8 mg to about 10 mg daily. In some embodiments, the glucocorticoid is methylprednisolone and is administered at a dose of at least about 2 mg/kg.

In some embodiments, the additional therapeutic agent is an anti-T cell directed therapy. In some embodiments, the anti-T cell directed therapy is tocilizumab, canakinumab, or any combination thereof.

In one embodiment, the additional therapeutic agent is an immunomodulator. In one embodiment, the additional therapeutic agent is an immune checkpoint inhibitor. In one embodiment, the additional therapeutic agent is a TIM-3 inhibitor. In one embodiment, the TIM-3 inhibitor is MBG453. In one embodiment, the additional therapeutic agent is a LAG-3 inhibitor. In one embodiment, the LAG-3 inhibitor is LAG525. In one embodiment, the additional therapeutic agent is a PD-1 inhibitor. In one embodiment, the PD-1 inhibitor is PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, BGB-A317, BGB-108, INCSHR1210, or AMP-224. In one embodiment, the PD-1 inhibitor is PDR001. In one embodiment, the PD-1 inhibitor is administered at a dose of about 100 mg once every four weeks, or about 200 mg once every four weeks, or about 300 mg once every four weeks, or about 400 mg once every four weeks, or about 500 mg once every four weeks. In one embodiment, the PD-1 inhibitor is administered at a dose of about 400 mg once every four weeks.

The additional therapeutic agent can be administered in any effective way. For example, the additional therapeutic agent can be administered orally. In another embodiment, the additional therapeutic agent can be administered intravenously.

The BCMA binding molecule and/or GSi and/or the one or more additional therapeutic agents can prevent or treat cancer. In one embodiment, the cancer is a blood cancer. In one embodiment, the blood cancer is multiple myeloma.

10. THERAPEUTIC INDICATIONS

5 The BCMA binding molecules and/or GSi of the disclosure can be used in the treatment of any disease associated with BCMA expression. In one aspect, the disclosure provides a method of treating cancer in a subject. The method comprises administering to the subject a BCMA binding molecule and/or GSi such that the cancer is treated in the subject. An example
10 of a cancer that is treatable by the BCMA-targeting agent and/or GSi is a cancer associated with expression of BCMA, such as multiple myeloma (also known as MM) (See Claudio *et al.*, 2002, *Blood*. 100(6):2175-86; and Novak *et al.*, 2004, *Blood*. 103(2):689-94). Multiple myeloma, also known as plasma cell myeloma or Kahler's disease, is a cancer characterized by an accumulation of abnormal or malignant plasma B-cells in the bone marrow. Frequently, the cancer cells invade adjacent bone, destroying skeletal structures and resulting in bone pain
15 and fractures. Most cases of myeloma also feature the production of a paraprotein (also known as M proteins or myeloma proteins), which is an abnormal immunoglobulin produced in excess by the clonal proliferation of the malignant plasma cells. Blood serum paraprotein levels of more than 30g/L is diagnostic of multiple myeloma, according to the diagnostic criteria of the International Myeloma Working Group (IMWG) (See Kyle *et al.*, 2009, *Leukemia*. 23:3-9). Other
20 symptoms or signs of multiple myeloma include reduced kidney function or renal failure, bone lesions, anemia, hypercalcemia, and neurological symptoms.

11. PATIENT POPULATION

The BCMA binding molecules and/or GSi can be used to treat subjects in need thereof. The subjects can be diagnosed with cancer, *e.g.*, a blood cancer such as multiple myeloma. In
25 one embodiment, the subject has relapsed and/or refractory multiple myeloma.

In some embodiments, the subject has been previously been treated for cancer. In some embodiments, the subjects can have previously been treated with one or more therapeutic agents. In some embodiments, the treatment may have failed.

In some embodiments, the subject has previously received one or more prior treatments
30 for their disease. In some embodiments, the subject has previously received one prior treatment for their disease. In some embodiments, the subject has previously received two prior treatments for their disease. In some embodiments, the subject has previously received three prior treatments for their disease. In some embodiments, the subject has previously received four or more prior treatments for their disease.

35 In some embodiments, the prior treatment regimens did not comprise a multispecific antibody (*e.g.*, a BCMA targeting multispecific antibody). In one embodiment, the prior

treatment regimens did not comprise a CAR-T (e.g., a BCMA targeting CAR-T). In one embodiment, the prior treatment regimens did not comprise a RLT (e.g., a BCMA targeting RLT).

5 In some embodiments, the subject previously received an immunomodulatory drug (IMiD), a proteasome inhibitor, an anti-CD38 antibody, or any combination thereof. In some embodiments, the subject previously received an IMiD. For example, the IMiD included lenalidomide, pomalidomide, or both. In some embodiments, the subject previously received a proteasome inhibitor. For example, the proteasome inhibitor included bortezomib, carfilzomib, or both. In some embodiments, the subject previously received an anti-CD38 antibody. For
10 example, the anti-CD38 antibody included daratumumab. In one embodiment, the prior treatment regimens included an autologous bone marrow transplant, a BCMA CAR-T, a BCMA antibody-drug conjugate, or any combination thereof.

In some embodiments, the subject that is treated with the BCMA binding molecule is not eligible for treatment with other anti-cancer regimens known to provide clinical benefit.

15 **11.1. Inclusion Criteria**

The subject that can be treated with the BCMA binding molecules and/or GSi can include a subject that has signed an informed consent form prior to being treated with the BCMA binding molecule and/or GSi.

20 The subject that can be treated with the BCMA binding molecules and/or GSi can include a subject that is a male or female subject that is greater than equal to 18 years of age.

The subject that can be treated with the BCMA binding molecules and/or GSi can include a subject that has an Eastern Cooperative Oncology Group (ECOG) performance status of less than equal to two (2). The ECOG performance status can be determined at any time prior to being treated with the BCMA binding molecule and/or GSi.

25 The subject that can be treated with the BCMA binding molecules and/or GSi can include a subject that has a confirmed diagnosis of cancer. For example, the subject that can be treated with the BCMA binding molecule and/or GSi can be a subject that has a confirmed diagnosis of multiple myeloma. The subject can also have received two or more standard of care (SoC) regimens. The SoC regimens can include an IMiD (e.g. lenalidomide or
30 pomalidomide), a proteasome inhibitor (e.g. bortezomib, carfilzomib), and/or an anti-CD38 agent (e.g. daratumumab. The subject can also be relapsed and/or refractory to, or intolerant of each regimen. The subject can also have documented evidence of disease progression (IMWG criteria) even after receiving previous treatments. The subject can have also previously received a prior autologous bone marrow transplant, a BCMA CAR-T or BCMA-ADC.

The subject that can be treated with the BCMA binding molecules and/or GSi can include a subject that has a measureable disease defined by serum M-protein level of greater than equal to 1.0 g/dL. The subject that can be treated with the BCMA binding molecules and/or GSi can include a subject that has a measureable disease defined by urine M-protein level of greater than equal to 200 mg/24 hours. The subject that can be treated with the BCMA binding molecules and/or GSi can include a subject that has a measureable disease defined by serum free light chain (sFLC) of greater than 100 mg/L of involved FLC.

The subject that can be treated with the BCMA binding molecules and/or GSi can include a subject that is willing to undergo a serial bone marrow aspirate and/or biopsy. The serial bone marrow aspirate and/or biopsy can occur at any time prior to treatment with the BCMA binding molecule and/or GSi. The serial bone marrow aspirate and/or biopsy can occur at any time following treatment with the BCMA binding molecule and/or GSi. The serial bone marrow aspirate and/or biopsy can be performed for the assessment of disease status and biomarker/pharmacodynamics.

11.2. Exclusion Criteria

In some embodiments, the subject that can be treated with the BCMA binding molecules and/or GSi may not have or have had one or more of the following exclusion criteria disclosed in this Section 11.2. For example, in some embodiments if the subject has or has had any one of the following exclusion criteria disclosed in this Section 11.2, then they should not be treated with the BCMA binding molecule and/or GSi. As another example, the subject that can be treated with the BCMA binding molecules and/or GSi may not have or have had two or more of the following exclusion criteria disclosed in this Section 11.2. As another example, the subject that can be treated with the BCMA binding molecules and/or GSi may not have or have had three or more of the following exclusion criteria disclosed in this Section 11.2. As another example, the subject that can be treated with the BCMA binding molecules and/or GSi may not have or have had four or more of the following exclusion criteria disclosed in this Section 11.2. As another example, the subject that can be treated with the BCMA binding molecules and/or GSi may not have or have had five or more of the following exclusion criteria disclosed in this Section 11.2.

The subject that can be treated with the BCMA binding molecules and/or GSi can include a subject that may not have had previous radiotherapy. In other embodiments, the subject may have had previous radiotherapy. In some embodiments, the radiotherapy was not done within one month of the start of treatment. In some embodiments, the radiotherapy was not done within three weeks of the start of treatment. In some embodiments, the radiotherapy was not done within two weeks of the start of treatment. In some embodiments, the radiotherapy was not done within one week of the start of treatment.

Some exceptions for previous radiotherapy can be made, for example if the radiotherapy was localized. For example, the localized radiotherapy can have been for bone lesions, such as lytic bone lesions. Or in some cases, the localized radiotherapy can have been for phasmyctomas. Under these circumstances, the subject can be eligible for the treatment with the BCMA binding molecule and/or GSi.

The subject that can be treated with the BCMA binding molecules and/or GSi can include a subject that may not have had a recent major surgery. In some embodiments, the recent major surgery was not done within six months of the start of treatment. In some embodiments, the recent major surgery was not done within five months of the start of treatment. In some embodiments, the recent major surgery was not done within four months of the start of treatment. In some embodiments, the recent major surgery was not done within three months of the start of treatment. In some embodiments, the recent major surgery was not done within two months of the start of treatment. In some embodiments, the recent major surgery was not done within one month of the start of treatment. In some embodiments, the recent major surgery was not done within three weeks of the start of treatment. In some embodiments, the recent major surgery was not done within two weeks of the start of treatment. In some embodiments, the recent major surgery was not done within one week of the start of treatment.

The subject that can be treated with the BCMA binding molecules and/or GSi can include a subject that may not be using steroid therapy. In some embodiments, the steroid can be prednisone, dexamethasone, cortisol, equivalents thereof, or any other corticosteroids for human use. In some embodiments, the steroid therapy should not be chronic steroid therapy. For example, daily use of greater than equal to 10 mg of prednisone or equivalents can be considered chronic steroid therapy.

Some exceptions can be made if the steroids are topical, inhaled, nasal, or ophthalmic. Under these circumstances, the subject can be eligible for the treatment with the BCMA binding molecule and/or GSi.

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that may not be using any immunosuppressive therapy/medication. In some embodiments, the immunosuppressive therapy/medication may not have been given within a month of treatment with the BCMA binding molecule and/or GSi. In some embodiments, the immunosuppressive therapy/medication may not have been given within four weeks of treatment with the BCMA binding molecule and/or GSi. In some embodiments, the immunosuppressive therapy/medication may not have been given within three weeks of treatment with the BCMA binding molecule and/or GSi. In some embodiments, the immunosuppressive therapy/medication may not have been given within two weeks of

treatment with the BCMA binding molecule and/or GSi. In some embodiments, the immunosuppressive therapy/medication may not have been given within one week of treatment with the BCMA binding molecule and/or GSi. In some embodiments, the immunosuppressive medication is not a systemic treatment.

5 With regards to steroid therapy and/or immunosuppressive therapy, these considerations are independent of the potential pre-treatment, co-treatment, or post-treatment with immune suppressors in order to prevent/ameliorate any side effects (such as CRS) that is associated with treatment with a BCMA binding molecule and/or GSi. In other words, a person who is pre-/co-/post- with an immunosuppressive therapy as a part of the treatment regimen
10 that comprises a BCMA binding molecule and/or GSi can still be eligible for the treatment with the BCMA binding molecule and/or GSi.

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that may not have used any BCMAxCD3 bispecific antibody therapies in the past.

15 The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that may not have or have had a history of hypersensitivity reaction to any ingredient that contains the BCMA binding molecule and/or GSi. For example, the subject may not have or have had hypersensitivity reactions to any excipients in the formulation. In some
embodiments, the subject may not have or have had hypersensitivity reactions to other
monoclonal antibodies. In some embodiments, the hypersensitivity reactions are severe
20 hypersensitivity reactions.

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that may not have experienced toxicity with any previously treated BCMA targeted agents.

25 The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have any malignant disease except for the disease that is being treated with the BCMA binding molecule and/or GSi. In other words, the subject can include a subject that does not have two or more malignant diseases, one of which is not being treated by the BCMA binding molecule and/or GSi.

30 Some exceptions can be made if the malignancies were previously treated and a complete response/remission of the malignancy was observed. In other words, if the previous treatments for the malignancy were curative. In some embodiments, the malignancy has not recurred within the past five years. In some embodiments, the malignancy has not recurred within the past four years. In some embodiments, the malignancy has not recurred within the past three years. In some embodiments, the malignancy has not recurred within the past two
35 years. In some embodiments, the malignancy has not recurred within the past year. In some embodiments, the malignancy has not recurred within the past six months. Other exceptions

can include subjects who had completely resected basal cell and squamous cell skin cancers. Further exceptions can include completely resected carcinoma *in situ* of any type. Under these circumstances, the subject can receive treatment with the BCMA binding molecule and/or GSi.

5 The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have active autoimmune disease. The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that is not known to have an autoimmune disease. The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that is not suspected to have an autoimmune disease.

10 Some exceptions for autoimmune diseases can be made for subjects have vitiligo, hypothyroidism, or psoriasis. If the subject has hypothyroidism, the subject can have residual hypothyroidism. In some embodiments, if the subject has residual hypothyroidism, the subject that can be treated with the BCMA binding molecule and/or GSi only requires hormone replacement. If the subject has psoriasis, the subject that can be treated with the BCMA binding molecule and/or GSi does not require systemic treatment. In some embodiments, if the
15 subject has psoriasis, the condition is not expected to recur. Under these circumstances, the subject can receive treatment with the BCMA binding molecule and/or GSi.

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that has not been treated with a prohibited medication. In some embodiments, the subject has not been treated with a prohibited medication that cannot be discontinued at least
20 three months prior to the start of treatment. In some embodiments, the subject has not been treated with a prohibited medication that cannot be discontinued at least two months prior to the start of treatment. In some embodiments, the subject has not been treated with a prohibited medication that cannot be discontinued at least one month prior to the start of treatment. In some embodiments, the subject has not been treated with a prohibited medication that cannot
25 be discontinued at least four weeks prior to the start of treatment. In some embodiments, the subject has not been treated with a prohibited medication that cannot be discontinued at least three weeks prior to the start of treatment. In some embodiments, the subject has not been treated with a prohibited medication that cannot be discontinued at least two weeks prior to the start of treatment. In some embodiments, the subject has not been treated with a prohibited
30 medication that cannot be discontinued at least one week prior to the start of treatment. In some embodiments, the subject has not been treated with a prohibited medication that cannot be discontinued at least six days prior to the start of treatment. In some embodiments, the subject has not been treated with a prohibited medication that cannot be discontinued at least five days prior to the start of treatment. In some embodiments, the subject has not been
35 treated with a prohibited medication that cannot be discontinued at least four days prior to the start of treatment. In some embodiments, the subject has not been treated with a prohibited medication that cannot be discontinued at least three days prior to the start of treatment. In

some embodiments, the subject has not been treated with a prohibited medication that cannot be discontinued at least two days prior to the start of treatment. In some embodiments, the subject has not been treated with a prohibited medication that cannot be discontinued at least one day prior to the start of treatment.

- 5 The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have greater than equal to grade 2 neuropathy.

 The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have greater than or equal to grade 1 residual toxic effects from any previous therapy.

- 10 The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have plasma cell leukemia and other plasmacytoid disorders, other than multiple myeloma.

- The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have a clinical laboratory result of an absolute neutrophil count (ANC) of greater than 1,000/mm³ without growth factor support. This ANC count can be measured 1 month prior to the start of treatment. In some embodiments, the ANC count can be measured 4 weeks prior to the start of treatment. In some embodiments, the ANC count can be measured 3 weeks prior to the start of treatment. In some embodiments, the ANC count can be measured 2 weeks prior to the start of treatment. In some embodiments, the ANC count can be measured 1 week prior to the start of treatment. In some embodiments, the ANC count can be measured 6 days prior to the start of treatment. In some embodiments, the ANC count can be measured 5 days prior to the start of treatment. In some embodiments, the ANC count can be measured 4 days prior to the start of treatment. In some embodiments, the ANC count can be measured 3 days prior to the start of treatment. In some embodiments, the ANC count can be measured 2 days prior to the start of treatment. In some embodiments, the ANC count can be measured 1 day prior to the start of treatment.

- The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have a clinical laboratory result of a platelet count less than 75,000 mm³ without transfusion support. This platelet count can be measured 1 month prior to the start of treatment. In some embodiments, the platelet count can be measured 4 weeks prior to the start of treatment. In some embodiments, the platelet count can be measured 3 weeks prior to the start of treatment. In some embodiments, the platelet count can be measured 2 weeks prior to the start of treatment. In some embodiments, the platelet count can be measured 1 week prior to the start of treatment. In some embodiments, the platelet count can be measured 6 days prior to the start of treatment. In some embodiments, the platelet count can be measured 5 days prior to the start of treatment. In some embodiments, the platelet count can

be measured 4 days prior to the start of treatment. In some embodiments, the platelet count can be measured 3 days prior to the start of treatment. In some embodiments, the platelet count can be measured 2 days prior to the start of treatment. In some embodiments, the platelet count can be measured 1 day prior to the start of treatment.

5 The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have a clinical laboratory result of a bilirubin level that is greater than 1.5 times the upper limit of the normal range (ULN). In some embodiments, the bilirubin level can be greater than 1.1 times the ULN. In some embodiments, the bilirubin level can be greater than 1.2 times the ULN. In some embodiments, the bilirubin level can be greater than 1.3 times
10 the ULN. In some embodiments, the bilirubin level can be greater than 1.4 times the ULN. In some embodiments, the bilirubin level can be greater than 1.6 times the ULN. In some embodiments, the bilirubin level can be greater than 1.7 times the ULN. In some embodiments, the bilirubin level can be greater than 1.8 times the ULN. In some embodiments, the bilirubin level can be greater than 1.9 times the ULN. In some embodiments, the bilirubin level can be
15 greater than 2.0 times the ULN.

 The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have a clinical laboratory result of an aspartate aminotransferase (AST) level that is greater than 3 times the upper limit of the normal range (ULN). In some
 embodiments, the AST level can be greater than 1.5 times the ULN. In some embodiments, the
20 AST level can be greater than 2.0 times the ULN. In some embodiments, the AST level can be greater than 2.5 times the ULN. In some embodiments, the AST level can be greater than 3.5 times the ULN. In some embodiments, the AST level can be greater than 4.0 times the ULN. In some embodiments, the AST level can be greater than 4.5 times the ULN. In some
 embodiments, the AST level can be greater than 5.0 times the ULN.

25 The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have a clinical laboratory result of an alanine aminotransferase (ALT) level that is greater than 3 times the upper limit of the normal range (ULN). In some
 embodiments, the ALT level can be greater than 1.5 times the ULN. In some embodiments, the
 ALT level can be greater than 2.0 times the ULN. In some embodiments, the ALT level can be
30 greater than 2.5 times the ULN. In some embodiments, the ALT level can be greater than 3.5 times the ULN. In some embodiments, the ALT level can be greater than 4.0 times the ULN. In some embodiments, the ALT level can be greater than 4.5 times the ULN. In some
 embodiments, the ALT level can be greater than 5.0 times the ULN.

 The subject that can be treated with the BCMA binding molecule and/or GSi can include
35 a subject that does not have a clinical laboratory result of a calculated creatinine clearance less than 30 ml/min. In some embodiments, the calculated creatinine clearance less than 10

ml/min. In some embodiments, the calculated creatinine clearance less than 20 ml/min. In some embodiments, the calculated creatinine clearance less than 40 ml/min. In some embodiments, the calculated creatinine clearance less than 50 ml/min. The calculated creatinine clearance can be measured by any known method. For example, the Cockcroft-Gault equation can be used to calculate creatinine clearance.

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have impaired cardiac function. The subject that can be treated with the BCMA binding molecule and/or GSi does not have clinically significant cardiac disease. For example, the subject does not have clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (e.g., NYHA Grade ≥ 2), uncontrolled hypertension or clinically significant arrhythmia. In some embodiments, the subject does not have a QTcF > 470 msec on screening ECG or congenital long QT syndrome. In some embodiments, the subject does not have acute myocardial infarction or unstable angina pectoris less than 3 months prior to treatment.

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have an active infection. In some embodiments, the subject does not have an active infection that requires systemic therapy. In some embodiments, the subject does not have any severe infection within one month before treatment. In some embodiments, the subject does not have any severe infection within four weeks before treatment. In some embodiments, the subject does not have any severe infection within three weeks before treatment. In some embodiments, the subject does not have any severe infection within two weeks before treatment. In some embodiments, the subject does not have any severe infection within one week before treatment.

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes).

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have any prior allogeneic SCT.

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have human immunodeficiency virus (HIV infection).

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does not have active Hepatitis B (HBV) or Hepatitis C (HCV) infection. Some exceptions to the HBV/HCV requirement can be made if the disease is controlled under antiviral therapy. In some cases, the HBV/HCV is tested, for example, if the HBV or HCV is clinically indicated or if the patient has a history of HBV or HCV infection.

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that will not use any live vaccines against infectious diseases during the treatment period. In some embodiments, the subject will not use any live vaccines within 2 weeks of treatment commencement. In some embodiments, the subject will not use any live vaccines within 3 weeks of treatment commencement. In some embodiments, the subject will not use any live vaccines within 4 weeks of treatment commencement. In some embodiments, the subject will not use any live vaccines within 1 month of treatment commencement. In some embodiments, the subject will not use any live vaccines within 2 months of treatment commencement. In some embodiments, the subject will not use any live vaccines within 3 months of treatment commencement.

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that has not been treated with cytotoxic or small molecule targeted antineoplastics or any experimental therapy before treatment. In some embodiments, the subject has not been treated with the cytotoxic or small molecule targeted antineoplastics or any experimental therapy within 1 month prior to commencing treatment with the BCMA binding molecule and/or GSi. In some embodiments, the subject has not been treated with the cytotoxic or small molecule targeted antineoplastics or any experimental therapy within 4 weeks prior to commencing treatment with the BCMA binding molecule and/or GSi. In some embodiments, the subject has not been treated with the cytotoxic or small molecule targeted antineoplastics or any experimental therapy within 3 weeks prior to commencing treatment with the BCMA binding molecule and/or GSi. In some embodiments, the subject has not been treated with the cytotoxic or small molecule targeted antineoplastics or any experimental therapy within 2 weeks prior to commencing treatment with the BCMA binding molecule and/or GSi. In some embodiments, the subject has not been treated with the cytotoxic or small molecule targeted antineoplastics or any experimental therapy within 1 week prior to commencing treatment with the BCMA binding molecule and/or GSi. In some embodiments, the subject has not been treated with the cytotoxic or small molecule targeted antineoplastics or any experimental therapy within 10 half-lives prior to commencing treatment with the BCMA binding molecule and/or GSi. In some embodiments, the subject has not been treated with the cytotoxic or small molecule targeted antineoplastics or any experimental therapy within 7 half-lives prior to commencing treatment with the BCMA binding molecule and/or GSi. In some embodiments, the subject has not been treated with the cytotoxic or small molecule targeted antineoplastics or any experimental therapy within 5 half-lives prior to commencing treatment with the BCMA binding molecule and/or GSi. In some embodiments, the subject has not been treated with the cytotoxic or small molecule targeted antineoplastics or any experimental therapy within 4 half-lives prior to commencing treatment with the BCMA binding molecule and/or GSi. In some embodiments, the subject has not been treated with the cytotoxic or small molecule targeted antineoplastics or any experimental therapy within 3 half-lives prior to commencing treatment with the BCMA binding molecule and/or GSi.

antineoplastics or any experimental therapy within 3 half-lives prior to commencing treatment with the BCMA binding molecule and/or GSi. In some embodiments, the subject has not been treated with the cytotoxic or small molecule targeted antineoplastics or any experimental therapy within 2 half-lives prior to commencing treatment with the BCMA binding molecule and/or GSi.

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that has not had the initiation of hematopoietic colony-stimulating growth factors (*e.g.* G-CSF, M-CSF), thrombopoietin mimetics or erythroid stimulating agents less than or equal to two weeks prior to start of treatment. In some cases, the initiation did not occur less than one month prior to the start of treatment. In some cases, the initiation did not occur less than four weeks prior to the start of treatment. In some cases, the initiation did not occur less than three weeks prior to the start of treatment. In some cases, the initiation did not occur less than one week prior to the start of treatment.

If the subject received thrombopoietin mimetics more than two weeks prior to the treatment of the BCMA binding molecule and/or GSi, and the subject is on a stable dose, they can receive the BCMA binding molecule and/or GSi.

The subject that can be treated with the BCMA binding molecule and/or GSis and/or GSi can include a subject that has not received GM-CSF.

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that has not received intravenous IG infusions that were given for infection prophylaxis. In some embodiments, the IG infusions should have ended 3 months prior to the start of treatment with the BCMA binding molecule and/or GSi. In some embodiments, the IG infusions should have ended 2 months prior to the start of treatment with the BCMA binding molecule and/or GSi. In some embodiments, the IG infusions should have ended 1 month prior to the start of treatment with the BCMA binding molecule and/or GSi. In some embodiments, the IG infusions should have ended 4 weeks prior to the start of treatment with the BCMA binding molecule and/or GSi. In some embodiments, the IG infusions should have ended 3 weeks prior to the start of treatment with the BCMA binding molecule and/or GSi. In some embodiments, the IG infusions should have ended 4 weeks prior to the start of treatment with the BCMA binding molecule and/or GSi. In some embodiments, the IG infusions should have ended 1 week prior to the start of treatment with the BCMA binding molecule and/or GSi.

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does that have active central nervous system (CNS) involvement by malignancy or presence of symptomatic CNS metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery), or increasing doses of corticosteroids within 2 weeks prior to the start of treatment. In some embodiments, the CNS issues should not have

occurred 3 months prior to the start of treatment. In some embodiments, the CNS issues should not have occurred 2 months prior to the start of treatment. In some embodiments, the CNS issues should not have occurred 1 month prior to the start of treatment. In some embodiments, the CNS issues should not have occurred 4 weeks prior to the start of treatment.

- 5 In some embodiments, the CNS issues should not have occurred 3 weeks prior to the start of treatment. In some embodiments, the CNS issues should not have occurred 1 week prior to the start of treatment.

- The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that does have any serious medical or psychiatric illness likely to interfere with treatment with the BCMA binding molecule and/or GSi.
- 10

The subject that can be treated with the BCMA binding molecule and/or GSi can include a subject that is not pregnant or nursing (lactating). Pregnancy can be defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

- 15 The subject that can be treated with the BCMA binding molecule and/or GSi is, in some embodiments, not a woman of child-bearing potential, unless they are using effective methods of contraception (*e.g.*, two) during dosing and for 6 months after the last dose of study drug, including one highly effective method. A woman of child-bearing potential can be defined as all women physiologically capable of becoming pregnant. Women can be considered post-
- 20 menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (*i.e.* age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by
- 25 follow up hormone level assessment is she considered not of child bearing potential.

- Highly effective contraception methods include but are not limited to total abstinence, female sterilization, male sterilization, and use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), and other forms of hormonal contraception that have comparable efficacy (failure rate <1%) (*e.g.*,
- 30 hormone vaginal ring or transdermal hormone contraception). Other effective method of contraception include barrier methods of contraception such as condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide. (*e.g.*, foam, gel, film, cream, or vaginal suppository).

- With regards to abstinence, periodic abstinence (*e.g.*, calendar, ovulation, symptothermal, post-ovulation methods)) and withdrawal are not acceptable methods of
- 35 contraception.

With regards to female sterilization, examples include but are not limited to surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

5 Regarding male sterilization, this must have occurred at least 6 months prior to screening. For female subjects, the vasectomized male partner should be the sole partner for that subject.

 Regarding the use of oral contraception, in some embodiments, women must have been stable on the same pill for a minimum of three months before the commencement of treatment
10 with the BCMA binding molecule and/or GSi.

12. CLINICAL TRIALS

12.1. Study Design

 This is a first in human, phase I, multicenter, open-label study to determine the safety and efficacy of BSBM3 (a bispecific antibody that specifically binds to BCMA and CD3, as
15 described in throughout the disclosure) alone and in combination with AL-102 in subjects with multiple myeloma who have received two or more standard of care (SoC) lines of therapy including an IMiD (e.g. lenalidomide or pomalidomide), a proteasome inhibitor (e.g. bortezomib, carfilzomib), and an anti-CD38 agent (e.g. daratumumab) and are relapsed and/or refractory to or intolerant of each regimen, with documented evidence of disease progression per
20 International Myeloma Working Group (IMWG) criteria and must not be eligible for treatment with other regimens known to provide clinical benefit, as determined by the investigator.

 This study consists of two dose escalation parts (Arms A and B), each followed by an expansion part. Once preliminary single-agent BSBM3 safety and tolerability is established, the dose escalation of the combination arm (BSBM3 and AL-102) will be initiated and will begin
25 with a BSBM3 dose at least one dose level lower than the single-agent dose that has been tested and deemed to be tolerated as a single agent. This dose combination must satisfy the EWOC (Escalation with Overdose Control) criteria.

 BSBM3 as a single agent will be initially administered on a weekly (Q1W) schedule. BSBM3 in combination will also be initially administered on a weekly (Q1W) schedule with AL-
30 102 being administered weekly on a 2-days on 5-days off schedule. Study drug treatment will continue until a subject experiences unacceptable toxicity, progressive disease as per IMWG or treatment is discontinued at the discretion of the investigator or the patient. The study design is summarized in **FIG. 6**. Alternative dosing schedules for BSBM3 (e.g. Q2W, Q3W, TIW) or AL-
102 may be implemented during the study if supported by emerging data including preliminary
35 PK, PD and efficacy findings from this ongoing trial. If clinically significant cytokine release

syndrome (CRS) or associated symptoms are observed during dose escalation, the option of a priming dose of BSBM3 may be introduced and subsequent dosing schedules modified.

Should additional schedules of administration of BSBM3 be explored in the single agent setting, those could potentially be explored in combination with AL-102 as well, provided that the safety of these additional schedules is preliminarily established in the BSBM3 single agent arm first, and that the cumulative dose of BSBM3 tested in combination with AL-102 does not exceed what has been tested and deemed to be tolerated in the single agent setting with the same dosing schedules.

The design of this phase I, open label study was chosen to characterize the safety and tolerability of single agent BSBM3 or BSBM3 in combination with AL-102 in subjects with relapsed and/or refractory multiple myeloma who have been treated with at least 2 prior regimens, and have received an IMiD, proteasome inhibitor, and anti-CD38 antibody (if available), and determine a recommended dose and regimen for future studies. Where necessary, the dose escalation allows the MTD of single agent BSBM3 and BSBM3 in combination with AL-102 to be established and will be guided by a Bayesian Logistic Regression Model (BLRM).

The BLRM is a well-established method to estimate the MTD in cancer subjects. The adaptive BLRM will be guided by the escalation with overdose control (EWOC) principle to control the risk of DLT in future subjects on study. The use of Bayesian response adaptive models for small datasets has been accepted by EMEA ("Guideline on clinical trials in small populations", February 1, 2007) and endorsed by numerous publications (Babb *et al.*, 1998, Stat Med; 17(10):1103-20); (Neuenschwander *et al.*, 2008, Stat Med; 27(13):2420-39); (Neuenschwander *et al.*, 2010, Clin Trials; 7(1):5-18); (Neuenschwander *et al.*, 2014, in A Bayesian Industry Approach to Phase I Combination Trials in Oncology. In Statistical Methods in Drug Combination Studies. Zhao W and Yang H (eds), Chapman & Hall/CRC, 2014), and its development and appropriate use is one aspect of the FDA's Critical Path Initiative.

The decisions on new dose levels are made by the Investigators and Novartis study personnel in a dose escalation meeting based upon the review of subject tolerability and safety information (including the BLRM derived estimates of DLT risk) along with PK, PD and preliminary activity information available at the time of the decision.

12.2. Dose Escalation

During dose escalation, subjects with relapsed and/or refractory MM will be treated with single agent BSBM3 (Arm A) or BSBM3 in combination with AL-102 (Arm B) until the MTD/RD of each is reached. In each arm, it is estimated approximately 20 subjects are required during escalation to define the MTD/RD. In the combination arm, an additional enrichment cohort of 1-6 patients with prior exposure to BCMA-directed therapies might be enrolled.

The safety (including the dose-DLT relationship) and tolerability of the study treatment will be assessed, and regimen(s) and dose(s) will be identified for use in the expansion part based on the review of these data. The RD will also be guided by the available information on PK, PD, and preliminary anti-tumor activity. The dose escalation will be guided by an adaptive Bayesian logistic regression model (BLRM) following the Escalation with Overdose Control (EWOC) principle. Subject enrollment into cohorts will be staggered.

12.3. Dose Expansion

Once the MTD(s)/RD(s) have been determined in each escalation part, additional subjects will be enrolled in the expansion part in order to further characterize the PK, PD, and safety profile of study drug and to assess the preliminary anti-tumor activity of single agent BSBM3 or BSBM3 in combination of AL-102. More than one dose level at Q1W schedule might be explored as RDs for expansion. In addition, alternative dosing schedules may be explored in the escalation part. RD(s) of new schedules might be declared.

In the expansion part, subjects with relapsed and/or refractory MM will be treated with single agent BSBM3 (Arm A) or BSBM3 in combination of AL-102 (Arm B). In each arm, the expansion part will enroll approximately 20 subjects. Enrollment may be halted early based on the ongoing review of data from the expansion cohort.

12.4. Study Periods

12.4.1. Screening Periods

Subjects will be evaluated against study inclusion and exclusion criteria Section 12.7.1 and Section 12.7.2.

Newly obtained bone marrow aspirate and/or biopsy if available will be required to be submitted to a Novartis designated laboratory for biomarker assessment at screening/baseline for all subjects enrolled in dose escalation and dose expansion.

12.4.2. Treatment Period

The treatment period will begin on Cycle 1 Day 1. For the purpose of scheduling and evaluations, a treatment cycle will consist of 28 days.

12.4.3. Follow-Up Period

All subjects will be followed for safety evaluations after the last dose of study drug.

12.4.4. Disease Progression Follow-Up

Subjects who discontinue the study for any reasons other than disease progression as per IMWG criteria will be followed for progression of disease or until the initiation of new anti-cancer therapy.

12.5. Purpose and timing of design adaptations

The dose escalation design foresees that decisions on future dose levels based on available data are taken at the end of each cohort. These are described in related to Section 12.11.2 and Section 12.22.

5 If, during dose escalation, 2 patients experience an event of Grade ≥ 3 infusion related reaction (IRR) or cytokine release syndrome (CRS), as defined in Section 12.11.6 of the protocol, that does not resolve to Grade ≤ 1 or baseline within 48 hours, a priming dose may be introduced and subsequent dosing schedules modified. The priming dose approach, a dosing
10 schedule employing a low initial dose followed by escalation of subsequent doses, has been adopted for a number of tumor-targeting antibody therapeutics. Recently published data for blinatumumab showed that step-wise dosing mitigated cytokine release and neurotoxicity (Goebeler *et al.*, 2013, Hematol Oncol. 31(Suppl. 1):Abstr 302; Nagorsen *et al.*, 2012, Pharmacol Ther 136(3):334-42; Viardot *et al.*, 2015, Blood (ASH Annual Meeting Abstracts) 2010: Abstr 2880). If a priming dose is used, the dose will be determined based on a review of
15 the available data and in agreement with Novartis and the Investigators.

The MTD/RD will be selected based on review by Novartis study personnel and Investigators of available safety and tolerability information along with PK, PD and efficacy data. If the priming dose schedule is implemented, a separate Bayesian hierarchical logistic regression model (BHLRM) will be constructed to assess the DLT risk with EWOC principle
20 along with PK, PD and efficacy data. The expansion part may then begin as specified in Section 12.1.

12.6. Risks and Benefits

Subjects with relapsed refractory multiple myeloma who have failed multiple prior lines of therapy have a high unmet medical need. A bispecific antibody such as BSBM3 offers these
25 patients the potential to receive beneficial therapy for incurable disease, and the addition of AL-102 is supposed to potentially enhance activity of the molecule and potentially increase benefit for patients with r/r MM.

This study aims to start with safe doses of study treatment based on available pre-clinical data. Additionally, doses to be tested are expected to be in the range where anti-MM
30 activity may be achieved.

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules, are included in this protocol. Recommended treatment of adverse events are provided in Section 12.11.6. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close
35 clinical monitoring, including monitoring for infusion reactions, cytokine release syndrome,

neurotoxicity, immunosuppression and associated infections, immuno-inflammatory reactions, tumor lysis syndrome, gastrointestinal toxicity, and elevated liver enzymes.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and must agree that in order to participate in the study they must adhere to the strict contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

12.7. Population

This study will be conducted in adult subjects with relapsed and/or refractory MM who have been treated with at least 2 prior treatment regimens, and have received an IMiD, proteasome inhibitor, and anti-CD38 antibody (if available) and must not be eligible for treatment with other regimens known to provide clinical benefit, as determined by the investigator.

The investigator or designee must ensure that only subjects who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

12.7.1. Inclusion Criteria

Subjects eligible for inclusion in this study must meet all of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Male or female subjects ≥ 18 years of age.
3. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 at screening.
4. Subjects with a confirmed diagnosis of multiple myeloma who have received two or more standard of care (SoC) regimens including an IMiD (e.g. lenalidomide or pomalidomide), a proteasome inhibitor (e.g. bortezomib, carfilzomib), and an anti-CD38 agent (e.g. daratumumab), if available, and are relapsed and/or refractory to or intolerant of each regimen, with documented evidence of disease progression (IMWG criteria) and must not be eligible for treatment with other regimens known to provide clinical benefit, as determined by the investigator. Subjects who have received a prior autologous bone marrow transplant a BCMA CAR-T, or BCMA-ADC therapy and otherwise meet the inclusion criteria are eligible for this study.
5. Must have measurable disease defined by at least 1 of the following 3 measurements:
 - i. Serum M-protein ≥ 1.0 g/dL; OR
 - ii. Urine M-protein ≥ 200 mg/24 hours: OR
 - iii. Serum free light chain (sFLC) > 100 mg/L of involved FLC

6. All subjects must be willing to undergo a mandatory serial bone marrow aspirate and/or biopsy at screening and subsequently following treatment for the assessment of disease status and biomarker/pharmacodynamics. Exceptions may be considered after documented discussion.

5 **12.7.2. Exclusion Criteria**

Subjects meeting any of the following criteria are not eligible for inclusion in this study:

1. Radiotherapy within 14 days before the first dose of study drug except localized radiation therapy for lytic bone lesions or plasmacytomas
2. Major surgery within 2 weeks before the first dose of study drug
- 10 3. Use of systemic chronic steroid therapy (≥ 10 mg /day of prednisone or equivalent), or any immunosuppressive therapy within 7 days of first dose of study treatment. Topical, inhaled, nasal, or ophthalmic steroids are allowed.
4. Prior use of BCMAxCD3 bispecific therapies
5. Subjects receiving systemic treatment with any immunosuppressive medication (other
- 15 than steroids as described above)
6. History of severe hypersensitivity reactions to any ingredient of study drug(s) and other mAbs and/or their excipients
7. Subjects with toxicity to prior BCMA targeted agents
8. Malignant disease, other than that being treated in this study. Exceptions to this
- 20 exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.
9. Active, known or suspected autoimmune disease other than subjects with vitiligo, residual hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic
- 25 treatment or conditions not expected to recur
10. Subjects who are currently receiving treatment with a prohibited medication that cannot be discontinued at least one week prior to the start of treatment
11. Ongoing interstitial lung disease (ILD) or pneumonitis of grade ≥ 2 ; or history of or ongoing ILD or pneumonitis of grade ≥ 2
- 30 12. Subjects with Grade ≥ 2 neuropathy, and residual toxic effects from previous therapy must have resolved to Grade ≤ 1 or baseline
13. Plasma cell leukemia and other plasmacytoid disorders, other than MM
14. Any of the following clinical laboratory results:

- Absolute neutrophil count (ANC) < 1,000/mm³ without growth factor support within 7 days prior to the start of treatment
 - Platelet count < 75,000 mm³ without transfusion support within 7 days prior to the start of treatment
- 5
- Bilirubin > 1.5 times the upper limit of the normal range (ULN)
 - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times the ULN
 - Calculated creatinine clearance < 30 ml/min according to Cockcroft-Gault equation
- 10
15. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
- Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (NYHA Grade ≥ 2), uncontrolled hypertension or clinically significant arrhythmia
- 15
- QTcF > 470 msec on screening ECG or congenital long QT syndrome
 - Acute myocardial infarction or unstable angina pectoris < 3 months prior to study entry
16. Active infection requiring systemic therapy or other severe infection within 2 weeks before the first dose of study drug
- 20
17. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes)
18. Prior allogeneic SCT at any time prior to signing informed consent for the study.
19. Human immunodeficiency virus (HIV infection)
20. Active Hepatitis B (HBV) or Hepatitis C (HCV) infection. Subjects whose disease is
- 25
- controlled under antiviral therapy should not be excluded. Testing for HBV or HCV status is not necessary unless clinically indicated or the patient has a history of HBV or HCV infection
21. Use of any live vaccines against infectious diseases (e.g. influenza, varicella, pneumococcus) within 4 weeks of initiation of study treatment
22. Treatment with cytotoxic or small molecule targeted antineoplastics, or any experimental
- 30
- therapy, within 14-days or 5 half-lives whichever is shorter before the first dose of study treatment. For subjects that received antibodies or immunotherapies other than daratumumab the washout period is 4 weeks prior to study treatment. Daratumumab is prohibited within 3 weeks prior to study treatment.

23. Initiation of hematopoietic colony-stimulating growth factors (e.g. G-CSF, M-CSF), thrombopoietin mimetics or erythroid stimulating agents ≤ 2 weeks prior to start of study treatment. If thrombopoietin mimetics or erythroid stimulating agents were initiated more than 2 weeks prior to the first dose of study treatment and the patient is on a stable dose, they can be maintained. GM-CSF is not permitted due to the possible exacerbation of CRS.
24. Intravenous IG infusions given for infection prophylaxis must be discontinued ≥ 28 days prior to start of study treatment
25. Active central nervous system (CNS) involvement by malignancy or presence of symptomatic CNS metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery), or increasing doses of corticosteroids within the 2 weeks prior to the start of study treatment.
26. Serious medical or psychiatric illness likely to interfere with participation in this clinical study
27. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
28. Sexually active males unless they use a condom during intercourse while taking AL-102 and for 12 weeks after last dose of AL-102 and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants must not donate sperm for the time period specified above.
29. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using two effective methods of contraception, including at least one highly effective method, at the time of informed consent, during dosing and for 6 months after the last dose of study drug.
- Highly effective methods of contraception:
- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods)) and withdrawal are not acceptable methods of contraception
 - Female sterilization (surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

- Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

Other effective methods of contraception:

- Barrier method of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

12.8. Study Treatment

12.8.1. Investigational and control drugs

For this study, the term “investigational drug” and “study treatment” refers to BSBM3 and/or AL-102. BSBM3 and AL-102 are provided by Novartis.

BSBM3 is supplied as Liquid in vial (LIVI) formulation and it is composed of 10 mg/mL BSBM3, 20 mM histidine, 240 mM sucrose, PS20 0.04%, pH 5.5 ±0.3. AL-102 is supplied in a capsule.

All dosages prescribed and administered to subjects and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Table 1 Investigational drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Dose	Frequency and/or Regimen	Supply Type
BSBM3 50mg/ 5 ml	Liquid in vial (LIVI) (concentrate for solution for infusion)	Intravenous use	3-600 mcg / kg	Weekly (QW)*	Open label bulk supply; vials
AL-102 0.3 mg, 2 mg	Capsule	Oral use**	2 mg (starting dose)	Weekly (2 days on 5 days off) */***/****	Open label patient kits; bottles
*Alternative dosing regimens may be implemented **AL-102 should be taken with water; no chewing *** On co-dosing days AL-102 should be administered orally 2 hours before the start of BSBM3 infusion **** AL-102 should be taken at approximately the same time on dosing days					

Exploration of alternative doses and/or dosing regimens of single agent BSBM3 or BSBM3 in combination with AL-102 may be examined in escalation, even after initiation of the expansion part at RD. If enrolling simultaneously, subjects would be assigned in an alternating fashion to cohorts across all the sites in this global study.

12.8.2. Treatment Duration

During the treatment period, the study treatment will continue to be administered unless the patient experiences unacceptable toxicity, has clinical evidence of disease progression by IMWG criteria as determined by the investigator, and/or treatment is discontinued at the discretion of the investigator or the subject.

12.9. Other Treatments

12.9.1. Concomitant Therapy

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrheal agents) and safety of the subject are allowed.

Subjects must be told to notify the investigational site about any new medications, herbal remedies and dietary supplements he/she takes after the start of the study treatment. All medications (other than study treatment), significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions), prior antineoplastic therapies including medications, radiotherapy, and surgery, administered during the study must be listed on the appropriate case report forms.

12.9.1.1. Permitted Concomitant Therapy

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrheal agents) and safety of the subject are allowed.

5 Subjects must be told to notify the investigational site about any new medications, herbal remedies and dietary supplements he/she takes after the start of the study treatment. All medications (other than study treatment), significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions), prior antineoplastic therapies including medications, radiotherapy, and surgery, administered during the study must be listed
10 on the appropriate case report forms.

12.9.1.2. Infusion Reactions

Subjects are to be pre-medicated with acetaminophen and diphenhydramine (or their equivalent as per local standard of care) before each dose of the investigational drug BSBM3. Patients should be hospitalized and observed for at least 48 hours post infusion and consistent
15 with local practice for their first dose of BSBM3 and any subsequent intra-patient dose escalation. If a subject experienced an infusion reaction, either an acute allergic response, infusion related reaction (IRR), or symptoms of cytokine release syndrome (CRS), he/she must be hospitalized for at least 48 hours on subsequent dosing days. Pre-medications should be chosen per institutional practice at the discretion of the treating physician.

20 If ≥ 2 subjects experience $\geq$ Grade 2 infusion reactions or CRS symptoms, despite the mandatory premedication outlined above, in any dose-escalation cohort on Cycle 1 Day 1 (C1D1), then additional mandatory primary prophylaxis regimens (i.e., before dosing on C1D1) will be instituted after discussion and agreement among Investigators and Novartis. Prophylaxis regimens may include some combination of steroids, or other anti-T cell directed therapy (e.g.,
25 tocilizumab, canakinumab).

Acute allergic reactions should be treated as clinically indicated per institutional practice or the dose modification guideline (Section 12.11.4). In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a subject experiences a Grade 4 anaphylactic/anaphylactoid reaction, the subject will discontinue
30 study treatment. Such acute allergic reactions will be reported to the Sponsor in an expedited manner. These should be designated as reportable SAEs regardless of hospitalization, as medically important events.

Subjects with moderate to severe signs and symptoms attributable to CRS should be managed with supportive care and administration of tocilizumab.

Subjects should be treated in a facility equipped for cardiopulmonary resuscitation. Appropriate resuscitation equipment should be available at the bedside and a physician readily available.

The CTCAE category of "Infusion-related reaction" should be used to describe BSBM3 infusion reactions when the adverse events are considered related to the infusion. These adverse events should not be reported as "Allergic reaction".

12.9.2. Prohibited Medication

During the course of the study, subjects may not receive other additional investigational drugs, agents, devices, chemotherapy, or any other therapies that may be active against cancer. Additionally, no other therapeutic monoclonal antibodies and no immunosuppressive medication or live vaccines should be administered while on this study.

Subjects who are on stable doses of allowable growth factors prior to starting the study may continue treatment during Cycle 1. Initiation of these supportive care agents during Cycle 1 is prohibited unless the patient experiences a DLT. After a DLT has occurred, or during cycle 2 or subsequent cycles, they may be used as per institutional practice following discussion with Novartis. GM-CSF is prohibited during the study due to possible exacerbation of CRS.

Intravenous IG infusions given as prophylaxis for infections are prohibited during study treatment administration and for 4 weeks prior to starting study treatment.

The use of systemic steroid therapy (at doses greater than 10 mg/day prednisone or equivalent) and other immunosuppressive drugs is not allowed, with the exception of:

- Prophylactic use for subjects with imaging contrast dye allergy.
- Replacement-dose steroids (defined as 10 mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids) in the setting of adrenal insufficiency.
- Transient exacerbations of chronic inflammatory conditions such as chronic obstructive pulmonary disease (COPD). Steroids must be reduced to 10 mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids prior to the next treatment with BSBM3.
- The treatment of study treatment-related infusion reactions or study treatment-related irAEs. Steroids must be reduced to ≤ 10 mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids prior to the next study treatment administration. Steroid administration for the treatment of CRS should follow the CRS Management Guidelines.

Permitted medications are to be used with caution during AL-102 treatment. These medications should be excluded from patient use if possible. If they must be given based on the investigator's judgment, then use with caution and consider a treatment interruption if the concomitant medication is only needed for a short time.

12.9.3. Rescue Medication

Rescue medications for management of CRS are described in Table 8. Suspected CRS toxicities are described in Table 7. All rescue medications, including steroids given to treat CRS, must be listed on the concomitant medication CRF.

5 12.10. Subject numbering, treatment assignment, randomization**12.10.1. Subject Numbering**

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the
 10 Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

12.10.2. Treatment assignment, randomization

15 Treatment will be open to subjects, investigator staff, persons performing the assessments, and the Novartis clinical trial team.

12.11. Dose escalation and dose modification**12.11.1. Dose escalation guidelines****12.11.1.1. Starting Dose**

20 The Phase I starting dose for single agent BSBM3 (Arm A) was proposed based on an integrated assessment of predicted pharmacokinetics, the proposed mechanism of action, in vitro potency (to inform a MABEL dosing approach) as well as consideration of circulating shed BCMA and in vivo safety in the cynomolgus monkey GLP toxicology study. The starting dose for single agent BSBM3 for subjects enrolled in this trial is 3 mcg/kg administered as a 2 hour
 25 intravenous infusion.

In the combination arm (Arm B), the starting dose of BSBM3 will be determined based on data from the single agent arm of the study (Arm A) and will be at least one dose level below the highest dose of single agent BSBM3 determined to be tolerated.

30 The starting dose of AL-102, when administered with BSBM3 in the combination arm (Arm B), will be 2 mg on a 2 days on / 5 days off schedule (BIW). This dose has been determined to be safe and will be escalated alternatingly with BSBM3.

Alternative dosing schedules may also be explored if deemed appropriate based on emerging PK and safety assessments. The starting dose of new schedule(s) will be equal or lower than the maximum total cycle dose that has been previously tested and met the EWOC

criteria of both BLRM models on the schedule(s) previously tested and the new schedule(s) following a discussion with participating Investigators during dose escalation teleconference.

12.11.1.2. Provisional dose levels

The BSBM3 starting dose and the dose levels that may be evaluated during this trial are described in the Table 2. Actual dose levels will be determined based on available toxicity, pharmacokinetic and pharmacodynamic data, guided by the BLRM, following a discussion with participating investigators during dose escalation teleconferences (Section 12.21). Dose escalation will continue until one or more MTDs or RDs are determined.

Table 2 Provisional dose levels for BSBM3

Dose level	Proposed dose*	Increment from previous dose
-1**	1 mcg/kg	-150%
1	3 mcg/kg	(starting dose)
2	6 mcg/kg	100%
3	12 mcg/kg	100%
4	24 mcg/kg	100%
5	48 mcg/kg	100%
6	96 mcg/kg	100%
7	192 mcg/kg	100%
8	384 mcg/kg	100%
9	600 mcg/kg	56.26%

*It is possible for additional and/or intermediate dose levels to be added during the course of the study. Cohorts may be added at any dose level below the MTD in order to better understand safety, PK or PD.

**Dose level -1 represents a treatment dose for subjects requiring a dose reduction from the starting dose level. No dose reduction below dose level -1 is permitted for this study.

As an option, a priming dose will be used if, during dose escalation, 2 patients experience an event of Grade ≥ 3 infusion related reaction (IRR) or cytokine release syndrome (CRS), as defined in Section 12.11.6 of the protocol, that does not resolve to Grade ≤ 1 or baseline within 48 hours, and upon agreement between Novartis and Investigators if determined to be clinically necessary. The priming dose will be selected at a dose level determined to be safe (the dose be at least one dose level lower than the maximum dose tested in the previous cohorts and meets the EWOC criteria). In addition, as an added safety measure, one third of the priming dose will be given on Day 1 and two thirds of the dose on Day 2. Once the priming dose level is determined, the dose levels that may be evaluated in the subsequent cohorts are defined relative to the priming dose and are listed in Table 3.1. For example, if the priming dose is defined to be 100 mcg/kg (i.e. dose level X in Table 3.1), the dose on Day 1 will be 33.33 mcg/kg and on Day 2 will be 66.66 mcg/kg. The third and subsequent infusions (on Day 8, 15 and 22) will be at 200 mcg/kg (i.e. dose level X+1, where X+1 is the next provisional dose level after X listed in Table 3.1). Actual dose levels will be determined based on available toxicity, pharmacokinetic and pharmacodynamic data following

a discussion with participating investigators during dose escalation teleconferences (Section 12.21). A separate BHLRM will be constructed to guide the dose escalation with EWOC criteria. Dose escalation will continue until one or more MTDs or RDs are determined.

Table 3.1 Provisional dose levels with priming dose for BSBM3

Cohort*	Day 1 [‡] (priming dose)	Day 2 [‡] (priming dose)	Day 8 [£]	Day 15	D22
P-1**	X*1/3	X*2/3	X	X+1	X+1
P1	X*1/3	X*2/3	X+1	X+1	X+1
P2	X*1/3	X*2/3	X+2	X+2	X+2
P3	X*1/3	X*2/3	X+3	X+3	X+3

*The priming dose will be split into 2 days. On Day 1, subject will receive 1/3 of the total priming dose X and on Day 2, the rest of 2/3 of the priming dose will be administered.

£The "X +1/+2/+3" dose levels refer to 1/2/3 dose levels higher than X according to the provisional dose table.

*It is possible for additional and/or intermediate dose levels to be added during the course of the study. Cohorts may be added at any dose level below the MTD in order to better understand safety, PK or PD.

**Cohort P-1 represent treatment doses for subjects requiring a dose reduction from the priming dose level where the dose on Day 8 does not escalate but stay the same as the total priming dose. No dose reduction below cohort P-1 is permitted for this study.

5

The priming dose level may be adapted if needed, in accordance with evolving trial safety and tolerability findings.

For the combination therapy, the provisional dose levels and schedule of BSBM3 and AL-102 are described in Table 3.2. Actual dose levels will be determined based on available toxicity, pharmacokinetic and pharmacodynamic data. Dose escalation will continue until one or more MTDs or RDEs are determined. Should additional schedules of administration of BSBM3 be explored in the single agent setting, those could potentially be explored in combination with BSBM3 as well, provided that the safety of these additional schedules is preliminarily established in the BSBM3 single agent arm first, and that the cumulative dose of BSBM3 tested in combination with AL-102 does not exceed what has been tested and deemed to be safe in the single agent setting with the same dosing schedule.

Table 3.2 Provisional dose levels for combination arm

Dose level	BSBM3 dose*	AL-102 dose	Increment from previous dose
-2	6 mcg/kg	0.9 mg	-100%
-1	12 mcg/kg	0.9 mg	-110%
1	12 mcg/kg	2 mg	(starting dose)
2	24 mcg/kg	2 mg	100%
3	48 mcg/kg	2 mg	100%
4	48 mcg/kg	4 mg	100%

Dose level	BSBM3 dose*	AL-102 dose	Increment from previous dose
5	96 mcg/kg	4 mg	100%
6	192 mcg/kg	4 mg	100%
7	384 mcg/kg	4 mg	100%
8	384 mcg/kg	6 mg	50%

1. *It is possible for additional and/or intermediate dose levels to be added during the course of the study.
2. **Dose level -1 represents a treatment dose level to be implemented in case the starting dose level is not tolerated. No dose reduction below dose level -2 is permitted for this study.

12.11.2. Guidelines for dose escalation and determination of MTD/RD

The dose escalation is conducted in order to establish the dose(s) of single agent BSBM3 or BSBM3 in combination with AL-102 to be used in the expansion part. Specifically, it is the one or more doses that in the view of Investigators and Novartis study personnel have the most appropriate benefit-risk as assessed by the review of safety, tolerability, PK, any available efficacy, and PD, taking into consideration the maximum tolerated dose (MTD).

The MTD is the highest dose estimated to have less than 25% risk of causing a dose-limiting toxicity (DLT) during the DLT evaluation period in more than 33% of treated subjects.

The dose(s) selected for the expansion part can be any dose equal to or less than the MTD, and may be declared without identifying the MTD.

Each dose escalation cohort in the single agent BSBM3 arm (Arm A) will start with 1 to 6 newly treated subjects. They must have adequate exposure and follow-up to be considered evaluable for dose escalation decisions (see Section 12.21.1 for criteria in the definition of the Dose Determining Set).

For dose escalation with AL-102 combination (Arm B), each cohort will start with 3 to 6 evaluable participants.

If any subject experiences a DLT during the DLT evaluation period, the minimum cohort size will be increased to three.

If one or more subjects discontinue and fail to meet the evaluability criteria, the replacement policy may be used to enroll additional subjects to the same cohort, in order to support the benefit-risk assessment.

For each cohort where the dose level on Cycle 1 Day 1 is higher than any dose previously tested and shown to be safe, a staggered approach for the first two subjects in a cohort will be utilized. Following dosing of the first subject, the next subject will be dosed a minimum of 72 hours after the previous subject is dosed. Following completion of this staggered dosing of the first two subjects, subsequent subjects will be treated without staggering, however, no more than 1 patient within a cohort will have their first infusion on any given day. Dose escalation decisions will be made when all subjects in a cohort have

completed the DLT evaluation period or discontinued. Decisions will be made by Investigators and Novartis study personnel in a dose-escalation teleconference, and will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study, including safety information, available PK, available PD and preliminary efficacy.

5 Any dose escalation decisions made by investigators and Novartis personnel will not exceed the dose level satisfying the EWOC principle by the Bayesian logistic regression model (BLRM). For any dose levels, the dose for the next escalation cohort will not exceed a 100% increase from the previously tested safe dose. For the combination dose escalation part, or BSBM3 and AL-102 will not be escalated at the same time. For example, if a decision is made
10 to escalate BSBM3 in the combination, dose level of AL-102 will remain the same as previously tested dose combination. Smaller increases in dose may be recommended by the Investigators and Sponsor upon consideration of all of the available clinical data.

To better understand the safety, tolerability, PK, PD or anti-tumor activity of single agent BSBM3 or BSBM3 in combination with AL-102, before or while proceeding with further
15 escalation, enrichment cohorts of 1 to 6 subjects may be enrolled at any dose level or dose combination at or below the highest dose or dose combination previously tested and shown to be safe. Subjects with prior exposure to BCMA-directed therapies (CAR-T and ADC) might be enrolled as a separate enrichment cohort of up to 6 subjects at the active combination dose.

To reduce the risk of exposing subjects to an overly toxic dose, if 2 subjects experience
20 a DLT in a new cohort, the BLRM will be updated with the most up-to-date new information from all cohorts, without waiting for all subjects from the current cohort to complete the evaluation period.

- If the 2 DLTs occur in an escalation cohort, enrollment to that cohort will stop, and the next cohort will be opened at a lower dose level that satisfies the EWOC criteria.
- 25 - If the 2 DLTs occur in an enrichment cohort, then upon re-evaluation of all relevant data, additional subjects may be enrolled into the open cohorts only if the dose still meets the EWOC criteria. Alternatively, if recruitment to the same dose cannot continue, a new cohort of subjects may be recruited to a lower dose that satisfies the EWOC criteria. Additionally, if 2 or more patients experience a DLT in a dosing cohort, the next
30 dose-escalation level will not be more than 50% above the previous dose level.

Even in the event that a dose is not deemed acceptable for newly enrolled subject, ongoing subjects may continue treatment at that dose level at the discretion of the investigator and Novartis if it is in the best interests of the subject.

Besides the scenario of 2 DLTs, the current dose being tested may be de-escalated
35 based on new safety findings, including but not limited to observing a DLT, before a cohort is

completed. Subsequent to a decision to de-escalate, re-escalation may occur if data in subsequent cohorts supports this (EWOC criteria are satisfied).

All dose decisions must be agreed by Investigators and Novartis study personnel.

12.11.2.1. Implementation of dose escalation decisions

5 To implement dose escalation decisions, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), the assessment of risk to future patients from the BLRM along with the EWOC principle, and the available PK and PD information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Drug
10 administration at the next higher dose level may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level.

12.11.2.2. Intra-Subject dose escalation

Intra-subject dose escalation is not permitted at any time within the first 2 cycles of
15 treatment. After the 2nd cycle is completed, individual subjects may be considered for treatment at a dose of single agent BSBM3 higher than the dose to which they were initially assigned. The same guidelines apply to subjects receiving BSBM3 in combination with AL-102, with escalation of only one of the investigational drugs at any one time. In order for a subject to be treated at a higher dose of BSBM3 or BSBM3 in combination with AL-102, he or she must have
20 tolerated the lower dose for at least 2 cycles of therapy (i.e. he or she must not have experienced any non-hematologic toxicity CTCAE grade ≥ 2 at the lower dose originally assigned). Moreover, the new, higher dose with which the subject is to be treated must be a dose that has completed evaluation, and has shown to satisfy the EWOC principle at the last dose escalation teleconference before the time of the intra-subject escalation. There is no limit
25 to the number of times a subject may have his or her dose of BSBM3 or BSBM3 in combination with AL-102 increased. For any further increase after the initial intra-subject dose escalation, the following rules apply: The subject must have experienced no CTCAE grade ≥ 2 toxicity over at least two cycles of therapy at the lower dose, and the higher dose being considered must have been fully evaluated and shown not to exceed the MTD. Consultation and agreement with
30 Novartis must occur prior to any intra-subject dose escalation occurring. Data from the first cycle of treatment at the new dose level will not be formally included into the statistical model describing the relationship between dose and occurrence of DLT. However, this data will be incorporated into the clinical assessment of safety within a dose escalation teleconference.

12.11.3. Definitions of dose limiting toxicities (DLTs)

35 A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value where the relationship to single agent BSBM3 or BSBM3 in combination with AL-102

- cannot be ruled out, and is not clearly related solely to disease progression or inter-current illness that occurs within the DLT evaluation period (Cycle 1: C1D1;C1D28) with single agent BSBM3 or BSBM3 in combination with AL-102 and meets any of the criteria included in Table 4. The National Cancer Institute Common Terminology Criteria for Adverse events (NCI
- 5 CTCAE) version 5.0 will be used for all grading. For the purpose of dose-escalation decisions, DLTs will be considered and included in the BLRM.

The investigator must notify the sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities.

Table 4 Criteria for defining dose-limiting toxicities

During dose escalation, any Grade 3, Grade 4, or Grade 5 AEs (CTCAE v.5.0) excluding toxicities clearly related to disease progression or inter-current illness, occurring during Cycle 1 are DLTs, EXCEPT:	
Fatigue	Grade 3 fatigue that resolves to $\leq$ Grade 1 or baseline within 7 days.
Fever	Grade 3 fever, in the absence of neutropenia that resolves within 7 days.
Gastrointestinal	Grade 3 nausea and vomiting that resolves to $\leq$ Grade 1 within 48 hours of starting optimal anti-emetic therapy.
	Grade 3 diarrhea that resolves within 7 days after starting optimal anti-diarrhea treatment, where colitis is not suspected.
Dermatologic	Grade 3 non bullous rash without epidermal detachment that resolves to $\leq$ Grade 1 within 7 days of starting treatment
Hematology	Grade 3 neutropenia $\leq$ 5 days
	Grade 3 thrombocytopenia without clinically significant bleeding
	Anemia clearly related to underlying disease
	Leucopenia (low WBC count) in the absence of dose limiting neutropenia
	Lymphopenia of any grade is not a DLT
Electrolytes	Grade 3 or 4 electrolyte abnormalities that resolve to $\leq$ Grade 2 within 72 hours
Musculoskeletal	Grade 3 asymptomatic increase in creatine kinase that resolves within 14 days in the absence of evidence of cardiac involvement
Infusion reaction/CRS	Grade 3 infusion reaction including cytokine release syndrome (as defined by the CRS revised grading system), that resolves to $\leq$ Grade 1 or baseline within 48 hours
The following Grade 2 AEs related to study treatment <u>are considered DLTs</u> :	
Ocular disorders	Grade 2 eye pain or reduction of visual acuity are DLTs if they do not respond to topical therapy and do not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy, OR if they require systemic treatment.
Pneumonitis	Grade 2 pneumonitis is a DLT if it does not resolve to $\leq$ Grade 1 within 7 days of starting corticosteroids.
Myocarditis	Grade 2 myocarditis is a DLT.

Colitis	Grade 2 colitis is a DLT if it persists > 7 days despite treatment with corticosteroids.
Hepatic	Grade 2 ALT or AST accompanied by bilirubin >1.5 x ULN is a DLT.
Dermatologic	Grade 2 bullous disease that does not resolve to ≤ Grade 1 within 7 days of starting corticosteroids is a DLT.
Other adverse events	Other clinically significant toxicities in cycle 1 may be considered to be DLTs by the Investigators and Novartis, even if not CTCAE Grade 3 or higher.
* Depending on the nature of the AE, there may be cases where immune-related Grade 2-3 AEs of any duration warrant declaration of a DLT and permanent study discontinuation (e.g. Stevens Johnson Syndrome (SJS)). DLT determination not already outlined in this table will be made on a case-by case basis after Investigator discussion with the Novartis Medical Monitor.	

12.11.4. Dose Modifications

For subjects who do not tolerate the protocol-specified dosing schedule, dose adjustments may be permitted in order to allow the patient to continue study treatment. The following guidelines need to be applied:

- 5 **Dose modifications for Arm A (BSBM3 Single agent):**
- If a patient experiences an AE meeting the criteria for DLT as outlined in Section 12.11.3 (including events occurring after cycle 1, which is after the DLT period), treatment should be withheld. Following resolution of the toxicity to grade 1 or to the patient's baseline value, the patient may resume study treatment at the same or a lower dose level
 - 10 assessed to be safe (or decreasing the dosing frequency) except as described below as pertaining to Grade 3 non-hematologic AEs, if there is no evidence of confirmed disease progression as per IMWG. A decision to resume study treatment following the occurrence of a DLT is at the discretion of the Investigator.
 - If a patient experiences a DLT during the first cycle they must undergo a dose reduction.
 - 15 • Outside of the DLT window, if the investigator considers it to be in the patient's best interest to resume therapy before the toxicity has resolved to grade 1, this may be permitted on a case by case basis, following a documented discussion with Novartis.
 - Overall, for adverse events of potential immune-related etiology (irAE) that do not recover to ≤ Grade 1 or baseline at a dose of immunosuppression of ≤ 10 mg/day
 - 20 prednisone or equivalent within 12 weeks after initiation of immunosuppressive therapy, BSBM3 must be permanently discontinued.
 - For all Grade 3 non-hematologic AEs, study drug should be interrupted and not resumed until the event improves to Grade ≤1. At that point, the study drug may be resumed at the next lower dose level.
 - 25 • The study drug should be permanently discontinued for any Grade 4 non-hematologic adverse event (both in the DLT evaluation period and at any time point during the study).

- For other dose modifications refer to Table 5.1. Any final decisions concerning dose modifications or permanently discontinuing the patient from study drug due to study drug related toxicities will occur after following a documented discussion with Novartis.
 - If a patient requires a dose delay for > 21 consecutive days due to BSBM3-related toxicity, the patient should be discontinued from study treatment. If there is documented evidence of clinical benefit from study treatment and, in the opinion of the Investigator, it is in the patient's best interest to continue treatment, and if no safety concerns are present, the patient may resume study treatment after documented discussion with Novartis.
- 10 All interruptions or change to study drug administration must be recorded on the appropriate case report form (CRF).

Table 5.1 Criteria for dose reduction / interruption and re-initiation of BSBM3 treatment for adverse drug reactions

Worst toxicity CTCAE^a grade	Recommended Dose Modification
Infusion reaction or hypersensitivity reaction	
Grade 1	Decrease infusion rate until recovery from the symptoms.
Grade 2	Stop infusion immediately, and keep line open. Follow institutional guidelines for the management and follow-up of infusion reaction. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then permanently discontinue study treatment.
Grade 3	Stop infusion immediately, and keep line open. Follow institutional guidelines for the management and follow-up of infusion reaction. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. If the AE recurs at the reinitiated slow rate of infusion, and despite oral or IV pre-medication, or if symptoms do not resolve within 72 hours then permanently discontinue study treatment.
Grade 4	Discontinue infusion immediately, and permanently discontinue study treatment Provide supplemental oxygen, fluids, and other resuscitative measures as needed. Monitor vital signs (e.g. blood pressure, pulse, respiration, and temperature) every 15 ± 5 minutes until resolution.
Cytokine Release Syndrome (CRS)	
Grade 2 or Grade 3	See instructions for Grade 2 and 3 Infusion Reaction above.
Grade 4	Permanently discontinue study treatment. Manage and follow-up CRS as per institutional guidelines.

	Take blood for cytokine measurements as specified in Section 12.15.4.5 – Laboratory evaluations.
Ocular (uveitis, eye pain, blurred vision)	
Grade 1	Continue study treatment without dose modification. Ophthalmology consultation.
Grade 2	Hold study treatment if does not respond to topical therapy and doesn't improved to grade 1 severity within 2 weeks of the initiation of local therapy or if requires systemic treatment Urgent ophthalmology consultation. Upon resolution to ≤ Grade 1 may consider resuming study treatment without dose reduction after discussion with the Novartis Medical Monitor and in consultation with ophthalmology.
Grade 3 or Grade 4	Discontinue study treatment. Urgent ophthalmology consultation.
Pulmonary (pneumonitis)	
Grade 1	Consider study treatment hold. Manage per institutional practice. Consider resuming study treatment upon radiographic evidence of improvement.
Grade 2	Hold study treatment if does not resolve to ≤ Grade 1 within 7 days of starting corticosteroids. Pulmonary and infection workup. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification.
Grade 3 or Grade 4	Permanently discontinue study treatment.
Cardiovascular	
ECG QTc-Interval prolonged; hypertension	
Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 or baseline (hypertension, QTc) or < 30 msec difference from baseline (QTc) within ≤ 7 days, may resume study treatment at a reduced dose after discussion with the Novartis Medical Monitor. Baseline ECG refers to the ECG(s) collected at screening.
Grade 4	Permanently discontinue study treatment.
Other cardiovascular disorders	
Grade 2 (except myocarditis)	Hold study treatment. Upon resolution to Grade ≤ 1 or baseline, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor.
Grade 2 myocarditis, or Grade ≥ 3 other cardiac disorders related to study treatment	Permanently discontinue study treatment.
Gastrointestinal	
Diarrhea/colitis*	
	For any grade of diarrhea/colitis, consideration of use of corticosteroid therapy may be made once an infectious cause of diarrhea/colitis has been ruled out.
Grade 1	May continue study treatment without dose modification. Manage per institutional standard guidelines which should include anti-diarrheal treatment, and hydration.
Grade 2	Hold study treatment if persists > 7 days despite treatment according to institutional standard guidelines. GI consultation. Upon resolution to ≤ Grade 1 and tapering of steroid requirement to ≤ 10 mg prednisone per day, resume study treatment without dose modification after discussion with the Novartis Medical Monitor.
Grade 3	Hold study treatment. GI consultation. Upon resolution to ≤ Grade 1 or baseline and tapering of steroid requirement to ≤ 10 mg prednisone per day, may resume study

	treatment at a reduced dose after discussion with the Novartis Medical Monitor.
Grade 4	Permanently discontinue study treatment.
AST and/or ALT elevation not related to CRS	
Grade 2 AST and/or ALT	Hold study treatment. Manage per institutional practice. Upon resolution to $\leq$ Grade 1 or baseline, consider resuming study treatment without dose modification.
Grade 2 transaminitis with bilirubin $>1.5 \times$ ULN (unless Gilbert's syndrome)	Discontinue study treatment.
Grade 3 AST and/or ALT	Hold study treatment. Manage per institutional practices. Upon resolution to $\leq$ Grade 1 or baseline within 7 days, may resume study treatment at a reduced dose after discussion with the Novartis Medical Monitor.
Grade 4 AST and/or ALT	Otherwise, permanently discontinue study treatment.
Grade 4 AST and/or ALT	Permanently discontinue study treatment.
Isolated total bilirubin elevation	
Grade 2	Hold study treatment. Upon resolution to $\leq$ Grade 1 or baseline, may continue study treatment without dose modification.
Grade 3	Hold study treatment. Upon resolution to $\leq$ Grade 1 or baseline, may resume study treatment at a reduced dose after discussion with the Novartis Medical Monitor.
Grade 4	Permanently discontinue study treatment.
Asymptomatic amylase and/or lipase elevation**	
Grade 3, not associated with symptoms or clinical manifestations of pancreatitis**	Continue study treatment. If levels do not resolve to $\leq$ Grade 2 within ≤ 14 days after the initial report, hold study treatment. Upon resolution to $\leq$ Grade 2, may resume study treatment without dose modification, after discussion with the Novartis Medical Monitor.
Grade 4, not associated with symptoms or clinical manifestations of pancreatitis**	Permanently discontinue study treatment
Pancreatitis	
Grade 2/radiologic evidence	Hold study treatment. Manage per institutional practice. Upon resolution to $\leq$ Grade 1, may resume study treatment without dose modification, if no clinical evidence of pancreatitis and after discussion with the Novartis Medical Monitor.
Grade 3 or Grade 4	Permanently discontinue study treatment.
Renal	
Serum creatinine	
Grade 2	Continue treatment but measure at least twice weekly
Grade 3	Hold treatment until returns to $\leq$ Grade 1 or baseline and may restart at lower dose. If treatment delay >21 days, discontinue treatment.
Grade 4	Permanently discontinue treatment
Musculoskeletal	
Grade 2	Hold study treatment. Consider resuming study treatment without dose modification upon resolution to $\leq$ Grade 1 with appropriate management.
Grade 3	May resume study treatment at a reduced dose upon resolution to $\leq$ Grade 1 or baseline after discussion with the Novartis Medical Monitor
Grade 4	Permanently discontinue study treatment.
Endocrine	
Hypothyroidism or hyperthyroidism	
Grade 2	May continue study treatment without dose modification.

Grade 3	Management according to institutional practice. Hold study treatment.
Grade 4	Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification. May resume therapy following resolution or control with physiologic hormone replacement.
Other endocrine disorders	
Grade 2	Hold study treatment. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification.
Grade 3	Upon resolution to Grade ≤ 1 or baseline may continue treatment at a reduced dose
Grade 4	Permanently discontinue study treatment.
Dermatology (rash)	
Grade 1	Continue study treatment without dose modification. Topical steroids, antihistamines, topical emollients
Grade 2	Hold for bullous disease that does not resolve to $\leq$ Grade 1 within 7 days of starting corticosteroids Topical or oral steroids, antihistamines. If study treatment is held and resolution to $\leq$ Grade 1, resume study treatment without dose modification.
Grade 3	Hold study treatment. Manage per institutional practice. After resolution to $\leq$ Grade 1 or baseline, may continue study treatment at a reduced dose after discussion with the Novartis Medical Monitor.
Grade 4	Permanently discontinue study treatment
Bullous dermatitis	Hold study treatment. Grade 1-2 bullous dermatitis: discussion with the Novartis Medical Monitor is required before considering resuming study treatment. Grade 3 bullous dermatitis: consider resuming therapy after expert consultation and documented discussion with the Novartis medical monitor. Grade 4 bullous dermatitis: discontinue study treatment
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	Permanently discontinue study treatment
Hematology	
Neutropenia (ANC)	
Grade 3	Continue treatment at current dose and re-check complete blood count at least twice weekly
Grade 4	If ≤ 5 consecutive days, continue treatment at current dose and re-check complete blood count at least twice weekly If > 5 consecutive days hold treatment until resolution to lower grade If treatment delay is ≤ 21 days, restart at lower dose If treatment delay is > 21 days, permanently discontinue treatment
Febrile neutropenia	
Grade 3 or Grade 4	Hold study treatment until fever resolves then follow guidance for non-febrile neutropenia. If treatment delay is ≤ 21 days, restart at lower dose If treatment delay is > 21 days, permanently discontinue treatment
Thrombocytopenia	
Grade 3	If ≤ 5 consecutive days, continue treatment at current dose and re-check complete blood count at least twice weekly. If > 5 consecutive days hold treatment until platelets $\geq 50K/mm^3$

	If clinically significant bleeding develops hold treatment until bleeding resolves and restart at lower dose. If treatment delay is ≤ 21 days, restart at lower dose If treatment delay is > 21 days, discontinue treatment
Grade 4	If ≤ 5 consecutive days, continue treatment at current dose and re-check complete blood count at least twice weekly If > 5 consecutive days hold treatment until platelets $\geq 50K/mm^3$ then restart at lower dose. If clinically significant bleeding develops hold treatment until bleeding resolves and restart at lower dose. If treatment delay is > 21 days, permanently discontinue treatment
Anemia	
Grade 3 or Grade 4	Treatment-related anemia does not require study treatment hold or discontinuation.
Lymphopenia	
Any grade	Treatment-related lymphopenia does not require study treatment hold or discontinuation.
Other laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 3	Hold study treatment. Upon resolution to $\leq$ Grade 1, resume study treatment without dose modification.
Grade 4	Isolated Grade 4 electrolyte abnormalities not associated with clinical sequelae and corrected after appropriate management within 72 hours of their onset do not require discontinuation. In the case of Grade 4 electrolyte imbalances associated with clinical sequelae, or not resolved to $\leq$ Grade 1 within 72 hours despite appropriate management, discontinue study treatment.
Other non-laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 2	Consider study treatment hold, at Investigator discretion. Upon resolution to $\leq$ Grade 1, resume study treatment without dose modification.
Grade 3	Hold study treatment. Upon resolution to $\leq$ Grade 1, resuming study treatment must be discussed with the Novartis Medical Monitor.
Grade 4	Permanently discontinue study treatment.
All dose modifications should be based on the worst preceding toxicity.	
^a Common Toxicity Criteria for Adverse Events (CTCAE)	
*Note: anti-diarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.	
**Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within one week of the first occurrence of any $\geq$ Grade 3 of amylase and/or lipase.	

Dose modifications for Arm B (BSBM3 in combination with AL-102)

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- If a patient experiences an AE meeting the criteria for DLT as previously outlined (including events occurring after cycle 1, which is after the DLT period), both drugs should be withheld. Following resolution of the toxicity to grade 1 or to the patient's baseline value, the patient may resume study treatment either at the same combination level, or at a reduced dose level. Toxicities clearly related to BSBM3 alone should be managed according to the dose modification guidelines.

- Given the mechanism of action of AL-102 in combination with BSBM3, if a toxicity clearly attributable to BSBM3 arises during treatment, AL-102 should not be resumed until BSBM3 infusions are resumed.
- If a patient experiences a DLT during the first cycle (DLT-evaluation period), they must undergo a dose reduction.
- Outside of the DLT window, if the investigator considers it to be in the patient's best interest to resume therapy before the toxicity has resolved to grade 1, this may be permitted on a case by case basis, following a documented discussion with Novartis.

10 Table 5.2 Criteria for dose reduction / interruption and re-initiation of BSBM3 and AL-102 treatment for adverse drug reactions (Arm B only)

Worst toxicity CTCAE^a grade	Recommended Dose Modification
Infusion Reaction or Hypersensitivity reactions	
Grade 1	Decrease rate of BSBM3 infusion until recovery of symptoms
Grade 2	Stop BSBM3 infusion immediately, and keep line open. Upon resolution to $\leq$ Grade 1, restart BSBM3 infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. Do not re-dose AL-102 upon restarting infusion. If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then permanently discontinue both study drugs
Grade 3	Stop BSBM3 infusion immediately, and keep line open. If symptoms resolve to $\leq$ Grade 1 within 48 hours, restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. Do not re-dose AL-102 upon restarting infusion. If the AE recurs at the reinitiated slow rate of infusion, and despite oral or IV pre-medication, then permanently discontinue both study drugs. If Grade 3 symptoms last more than 48 hours, upon resolution to $\leq$ Grade 1 restart infusion at 50% of previous rate under continuous observation and at a lower dose of BSBM3. If an interval of at least 48 hours has passed between restarting infusion and the last dose of AL-102, AL-102 can be administered prior to restarting BSBM3 infusion at the same dose level.
Grade 4	Discontinue BSBM3 infusion immediately, and permanently discontinue both study drugs Provide supplemental oxygen, fluids, and other resuscitative measures as needed. Monitor vital signs (e.g. blood pressure, pulse, respiration, and temperature) every 15 $\pm$ 5 minutes until resolution.

Worst toxicity CTCAE ^a grade	Recommended Dose Modification
Cytokine Release Syndrome (CRS)	
Grade 2 or Grade 3	See instructions for Grade 2 and 3 Infusion Reaction above
Grade 4	Permanently discontinue both study drugs. Follow-up CRS as per institutional guidelines. Take blood for cytokine measurements – Laboratory evaluations.
Gastrointestinal	
Diarrhea/colitis*	
	For any grade of diarrhea/colitis, consideration of use of corticosteroid therapy may be made once an infectious cause of diarrhea/colitis has been ruled out. Treatment with loperamide (or other antidiarrheal treatment) should be initiated at the earliest onset of symptoms. For subjects who cannot tolerate loperamide or do not get adequate relief with maximum doses, standard doses of atropine may be added or used instead of loperamide. Additional antidiarrheal measures, such as octreotide, may be used at the discretion of the investigator or treating physician.
Grade 1	May continue study treatment without dose modification. Manage per institutional standard guidelines which should include anti-diarrheal treatment (loperamide or other), and hydration.
Grade 2	Hold both BSBM3 and AL-102 if persists > 7 days despite treatment according to institutional standard guidelines. GI consultation. Upon resolution to ≤ Grade 1 and tapering of steroid requirement to ≤ 10 mg prednisone per day, resume BSBM3 and AL-102 without dose modification after discussion with the Novartis Medical Monitor.
Grade 3	Hold both BSBM3 and AL-102. GI consultation. Upon resolution to ≤ Grade 1 or baseline and tapering of steroid requirement to ≤ 10 mg prednisone per day, may resume BSBM3 at the same dose and AL-102 at a reduced dose after discussion with the Novartis Medical Monitor. Upon re-occurrence of Grade 3 diarrhea, permanently discontinue AL-102 and continue BSBM3 treatment only.
Grade 4	Permanently discontinue BSBM3 and AL-102.

Worst toxicity CTCAE ^a grade	Recommended Dose Modification
AST and/or ALT elevation not related to CRS	
Grade 2 AST and/or ALT	Hold BSBM3 and AL-102. Manage per institutional practice. Upon resolution to $\leq$ Grade 1 or baseline, resume BSBM3 and AL-102 without dose modification.
Grade 3 AST and/or ALT	Hold BSBM3 and AL-102. Manage per institutional practices. Upon resolution to $\leq$ Grade 1 or baseline within 7 days, may resume BSBM3 and AL-102 at a reduced dose after discussion with the Novartis Medical Monitor. Dose reduction of AL-102 should be considered before changing the dose of BSBM3. Otherwise, discontinue BSBM3 and AL-102.
Grade 4 AST and/or ALT	Permanently discontinue BSBM3 and AL-102.
Grade 2 or higher transaminitis with bilirubin $>1.5 \times$ ULN (unless Gilbert's syndrome)	Permanently discontinue BSBM3 and AL-102.
Isolated total bilirubin elevation	
Grade 2	Hold BSBM3 and AL-102. Upon resolution to $\leq$ Grade 1 or baseline, may continue BSBM3 and AL-102 without dose modification.
Grade 3	Hold BSBM3 and AL-102. Upon resolution to $\leq$ Grade 1 or baseline, may resume BSBM3 and AL-102 at a reduced dose after discussion with the Novartis Medical Monitor. Dose reduction of AL-102 should be considered before changing the dose of BSBM3.
Grade 4	Discontinue BSBM3 and AL-102.

Worst toxicity CTCAE ^a grade	Recommended Dose Modification
Asymptomatic amylase and/or lipase elevation**	
Grade 3, not associated with symptoms or clinical manifestations of pancreatitis**	Continue BSBM3 and AL-102. If levels do not resolve to $\leq$ Grade 2 within $\leq$ 14 days after the initial report, hold BSBM3 and AL-102. Upon resolution to $\leq$ Grade 2, may resume BSBM3 and AL-102 without dose modification, after discussion with the Novartis Medical Monitor. If grade 3 elevations re-occurs, dose reduction of AL-102 should be considered before modifying the dose of BSBM3.
Grade 4, not associated with symptoms or clinical manifestations of pancreatitis**	Discontinue BSBM3 and AL-102
Pancreatitis	
Grade 2/radiologic evidence	Hold BSBM3 and AL-102. Manage per institutional practice. Upon resolution to $\leq$ Grade 1, may resume BSBM3 and AL-102 without dose modification, if no clinical evidence of pancreatitis and after discussion with the Novartis Medical Monitor.
Grade 3 or Grade 4	Permanently discontinue BSBM3 and AL-102.
Renal	
Serum creatinine	
Grade 2	Continue treatment with both drugs but measure at least twice weekly
Grade 3	Hold both study drugs until returns to $\leq$ Grade 1 or baseline and then restart both drugs with a dose reduction to one dose level below. If treatment delay >21 days, permanently discontinue study treatment.
Grade 4	Permanently discontinue treatment
Cardiovascular	
ECG QTc-Interval prolonged; hypertension	

Worst toxicity CTCAE^a grade	Recommended Dose Modification
Grade 3	Hold study treatment. Correction of underlying electrolyte abnormalities and hydration with other supportive measures. Upon resolution to Grade ≤ 1 or baseline (hypertension, QTc) or < 30 msec difference from baseline (QTc) within ≤ 7 days, may resume study treatment at a reduced dose of both drugs after discussion with the Novartis Medical Monitor. Baseline ECG refers to the ECG(s) collected at screening.
Grade 4	Permanently discontinue treatment.
Dermatology (rash) All grades	
Grade 2 and 3 or recurrent rashes	Consider supportive therapy with emollients, topical steroids, or antibiotics for potential superinfection. Consider a dose reduction of AL-102. No action is required for BSBM3.
Hematology	
Neutropenia (ANC)	
Grade 3	Check complete blood count at least twice weekly. If ≤ 5 consecutive days, continue BSBM3 and AL-102 at current dose and re-check complete blood count at least twice weekly. If > 5 consecutive days, hold treatment until resolution to $\leq$ Grade 2 and restart BSBM3 and AL-102 at one dose level below. If treatment delay is > 21 days, permanently discontinue BSBM3 and AL-102
Grade 4	Hold BSBM3 and AL-102. Check complete blood count at least twice weekly. Upon resolution to $\leq$ Grade 2, restart BSBM3 and AL-102 at one dose level below. If treatment delay is > 21 days, permanently discontinue BSBM3 and AL-102
Febrile neutropenia	
Grade 3 or Grade 4	Hold study BSBM3 and AL-102 until fever resolves then follow guidance for non-febrile neutropenia. If treatment delay is ≤ 21 days, restart BSBM3 and AL-102 at one dose level below. If treatment delay is > 21 days, permanently discontinue BSBM3 and AL-102
Thrombocytopenia	

Worst toxicity CTCAE^a grade	Recommended Dose Modification
Grade 3	If ≤ 5 consecutive days, continue BSBM3 and AL-102 at current dose and re-check complete blood count at least twice weekly. If > 5 consecutive days, hold both drugs until platelets ≥ 50K/mm³, then restart at the same dose of both drugs. If clinically significant bleeding develops, hold BSBM3 and AL-102 until bleeding resolves and restart at lower dose. If treatment delay is ≤ 21 days, restart BSBM3 and AL-102 at one dose level below. If treatment delay is > 21 days, permanently discontinue BSBM3 and AL-102
Grade 4	If ≤ 5 consecutive days, continue BSBM3 and AL-102 at current dose and re-check complete blood count at least twice weekly If > 5 consecutive days hold BSBM3 and AL-102 until platelets ≥ 50K/mm³ then restart BSBM3 and AL-102 at lower dose. If clinically significant bleeding develops, hold BSBM3 and AL-102 until bleeding resolves then restart BSBM3 and AL-102 one dose level below. If treatment delay is > 21 days, discontinue BSBM3 and AL-102
Anemia	
Grade 3 or Grade 4	Treatment-related anemia does not require study treatment hold or discontinuation.
Lymphopenia	
Any grade	Treatment-related lymphopenia does not require study treatment hold or discontinuation.
Other laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 3	Hold BSBM3 and AL-102. Upon resolution to ≤ Grade 1, resume BSBM3 and AL-102 without dose modification. In case of recurrent symptomatic hypophosphatemia, hypokalemia and hypocalcemia not appropriately managed with electrolyte replacement, consider reducing AL-102 to one dose level below.
Grade 4	Isolated Grade 4 electrolyte abnormalities, not associated with clinical sequelae and corrected after appropriate management within 72 hours of their onset, do not require discontinuation. BSBM3 and AL-102 may be continued at same or lower dose after documented discussion with Novartis In the case of Grade 4 electrolyte imbalances associated with clinical sequelae, or not resolved to ≤ Grade 1 within 72 hours despite appropriate management, discontinue BSBM3 and AL-102.

Worst toxicity CTCAE ^a grade	Recommended Dose Modification
Other non-laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 2	Consider BSBM3 and AL-102 hold, at Investigator discretion. Upon resolution to ≤ Grade 1, resume BSBM3 and AL-102 without dose modification.
Grade 3	Hold BSBM3 and AL-102. Upon resolution to ≤ Grade 1, resuming BSBM3 and AL-102 must be discussed with the Novartis Medical Monitor.
Grade 4	Discontinue BSBM3 and AL-102.
All dose modifications should be based on the worst preceding toxicity.	
^a Common Toxicity Criteria for Adverse Events (CTCAE)	
*Note: anti-diarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.	
**Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within one week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase.	

12.11.5. Follow-up for toxicities

The emergence of Immune-Related AE (irAE) may be anticipated based on the mechanism of action of immunomodulatory therapies.

- 5 An irAE is any clinically significant adverse event affecting any organ that is associated with study drug exposure, is consistent with an immune-mediated mechanism, and where alternative explanations have been investigated and ruled out or are considered to be unlikely. Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the Investigator or specialist consultant to verify the immune-related
- 10 nature of the AE. An empiric trial of corticosteroids may also contribute to understanding the etiology of a potential irAE.

Consensus management algorithms for irAEs have been developed and are available to assist investigators in assessing and managing irAEs (refer to Section 12.11.4).

- 15 Subjects whose treatment is interrupted or permanently discontinued due to an irAE, AE or clinically significant laboratory value, must be followed-up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.

- 20 All subjects must be followed up for irAEs, AEs and SAEs for 90 days following the last dose of BSBM3 alone or in combination.

12.11.6. Recommended treatment of adverse events

Subjects treated with BSBM3 alone or in combination may be at an increased risk of infusion reactions, cytokine release syndrome, neurotoxicity, immunosuppression and associated infections, immuno-inflammatory reactions, tumor lysis syndrome, gastrointestinal toxicity, and elevated liver enzymes. In general, treatment of adverse events should follow standard institutional practice. Additional guidance is provided below.

12.11.6.1. Cytokine Release Syndrome (CRS)

Ensure that at least 2 doses of tocilizumab per patient are available on site prior to infusion of BSBM3. Hospitals should have timely access to additional doses of tocilizumab.

Supportive care, tocilizumab, and corticosteroids have been used for effective management of CRS. Prompt responses to tocilizumab have been seen in most subjects.

Identify cytokine release syndrome (CRS) based on clinical presentation (see Table 6). Evaluate for and treat other causes of fever, hypoxia, and hypotension, monitor subjects for signs or symptoms of CRS for at least 4 weeks after treatment with BSBM3. Counsel subjects to seek immediate medical attention should signs or symptoms of CRS occur at any time.

At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab and/or corticosteroids as indicated.

A recommended treatment algorithm for the management of CRS is presented below in Table 7 and Table 8. The CRS management algorithm is a guideline and the investigator may use discretion or modify the treatment approach as needed for an individual subject.

Table 6 Clinical signs and symptoms associated with CRS (Lee *et al.*, 2014, Blood 124(2):188-95)

Organ system	Symptoms
Constitutional	Fever $\pm$ rigors, malaise, fatigue, anorexia, myalgia, arthralgia, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia $\pm$ bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures

Table 7 CRS Management

CRS severity	Symptomatic treatment	Tocilizumab	Corticosteroids
Mild symptoms requiring symptomatic treatment only e.g. low fever, fatigue, anorexia, etc.	Exclude other causes (e.g. infection) and treat specific symptoms with e.g. antipyretics, anti-emetics, anti-analgesics, etc. If neutropenic, administer antibiotics per local guidelines	Not applicable	Not applicable
Symptoms requiring moderate intervention: - high fever - hypoxia - mild hypotension	Antipyretics, oxygen, intravenous fluids and/or low dose vasopressors as needed.	If no improvement after symptomatic treatment administer tocilizumab i.v. over 1 hour: - 8 mg/kg (max. 800 mg) if body weight ≥ 30 kg - 12 mg/kg if body weight < 30 kg	If no improvement within 12-18 hours of tocilizumab, administer a daily dose of 2 mg/kg i.v. methylprednisolone (or equivalent) until vasopressor and oxygen no longer need, then taper.*
Symptoms requiring aggressive intervention: - hypoxia requiring high-flow oxygen supplementation or - hypotension requiring high-dose or multiple vasopressors	High-flow oxygen Intravenous fluids and high-dose vasopressor/s Treat other organ toxicities as per local guidelines	If no improvement, repeat every 8 hours (max total of 4 doses)*	
Life-threatening symptoms: - hemodynamic instability despite i.v. fluids and vasopressors - worsening respiratory distress - rapid clinical deterioration	Mechanical ventilation Intravenous fluids and high-dose vasopressor/s Treat other organ toxicities as per local guidelines		

* If no improvement after tocilizumab and steroids, consider other anti-cytokine and anti-T-cell therapies. These therapies may include siltuximab (11 mg/kg i.v. over 1 hour), high doses of steroids (e.g. high dose methylprednisolone or equivalent steroid dose according to local ICU practice) cyclophosphamide, anti-thymocyte globulin (ATG) or alemtuzumab.

Table 8 High Dose Vasopressors

Vasopressor	Dose to be given for ≥ 3 hours
Norepinephrine monotherapy	≥ 20 mcg/min
Dopamine monotherapy	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 200 mcg/min
Epinephrine monotherapy	≥ 10 mcg/min
If on vasopressin	Vasopressin + norepinephrine equivalent (NE) of ≥ 10 mcg/min*
If on combination vasopressors (not vasopressin)	NE of ≥ 20 mcg/min*

*Vasopressin and Septic Shock Trial (VASST) Norepinephrine Equivalent Equation:

NE dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷ 10] (Russell *et al.*, 2008, N Engl J Med; 358(9):877-87)

Other anti-cytokine therapies may also be considered upon their availability, if the subject does not respond to tocilizumab. If the subject experiences ongoing CRS despite administration of anti-cytokine directed therapies, anti-T-cell therapies such as cyclophosphamide, anti-thymocyte globulin (ATG) or alemtuzumab may be considered. These therapies need to be captured in appropriate CRFs.

The management of CRS is based solely upon clinical parameters as described in Table 8. Ferritin, CRP and serum cytokine levels should NOT be used for clinical management decisions. Cases of transient left ventricular dysfunction, as assessed by echocardiogram (ECHO), have been reported in some subjects with severe (Grade 4) CRS. Therefore consideration should be given to monitoring cardiac function by ECHO during severe CRS, especially in cases with prolonged severe hemodynamic instability, delayed response to high dose vasopressors, and/or severe fluid overload.

12.11.7. Neurological adverse events

Neurologic events, primarily reflective of encephalopathy and delirium, have been reported with CD3-engaging bispecific antibodies and may occur after BSBM3 infusion. These present clinically as signs and symptoms of varying severity including: confusion, disorientation, agitation, aphasia, somnolence and tremors. In severe cases seizures, motor weakness, incontinence, impaired consciousness, increased intracranial pressure, and cerebral edema may be concurrent to, following the resolution or in the absence of CRS. Subjects should be monitored for neurologic events, diagnostically worked-up and managed depending on the underlying pathophysiology and in accordance to local standard of care.

Evaluation:

- Thorough neurological examination, with frequent monitoring and determination of CTCAE grading, as well as ASBMT ICANS Consensus Grading (Lee *et al.*, 2019 Biol Blood Marrow Transplant, 25(4):625-638, doi: 10.1016/j.bbmt.2018.12.758. Epub 2018 Dec 25).
- Diagnostic work up to evaluate potential secondary causes:
 - Brain imaging (CT scan and/or MRI): to exclude intracranial hemorrhage, disease relapse, evidence suggestive of infection or cerebral edema.
 - Lumbar puncture for CSF evaluation, if applicable.
 - Chemistry laboratory testing
 - EEG

Management:

- If the neurological event is concurrent with CRS please refer to Table 8.
- Consider anti-seizure medications (e.g. levetiracetam) for patient at high risk (prior history of seizure) or administer in the presence of seizure
- For encephalopathy, delirium or associated events: appropriate treatment and supportive care should be implemented as per local standard of care. In worsening events, consideration should be given to the administration of a short course of steroids (Teachey, et. al 2018, Neelapu et. al 2018).

12.11.7.1. Hypersensitivity including acute infusion reactions

Subjects should be monitored for signs and symptoms of hypersensitivity following initiation of BSBM3 infusion and treated appropriately as per institutional guidelines. BSBM3 is contraindicated in subjects with known hypersensitivity to BSBM3 or to any component of the product formulation. If a subject experiences an infusion reaction and there is a concern for repeat toxicity during or after subsequent doses of BSBM3, in addition to providing maximum premedication, consider reducing the rate of infusion to 50% of the initial speed.

For patients in combination arm B, patient with an history of hypersensitivity to the excipients used in AL-102 are excluded from study.

Should emergency treatment be required in the event of life-threatening hypersensitivity or other infusion-related reaction, supportive therapy such as oxygen and drug treatment should be given according to local institutional guidelines. Subjects should be evaluated and carefully monitored until complete resolution of signs and symptoms.

12.11.7.2. Immunosuppression and associated infections

Due to immunodeficiency related to MM, including the existence of an exhausted T-cell phenotype at baseline, patients are at greater risk for bacterial and viral infections, including pneumonia, bacteremia, and sepsis (Blimark *et al.*, 2015, [citation missing from protocol; likely Haematologica. 100(1):107-13]). The use of CD3-engaging bispecific antibody may result in prolonged T-cell activation, potentially exacerbating the presence of an exhausted T-cell phenotype and further contributing to compromised T-cell immunity. Therefore, patients should have monitoring of complete blood counts and be monitored for signs and symptoms of infection while on study and during the 90 day post treatment follow-up period. Use infection precautions including antibiotic prophylaxis as appropriate and per local standard of care. As such, appropriate empiric, systemic antibiotic therapy should be considered and started when an infection is suspected as per local institutional guidelines for the treatment of infections in patients with MM.

Institutional guidelines for vaccination (e.g. pneumococcus) should be followed before starting BSBM3 therapy alone and in combination. No live vaccines should be used in BSBM3 recipients or prospective recipients.

12.11.7.3. Immuno-inflammatory Reactions

5 Inflammation may reflect rebound immuno-inflammatory reactions during immune reconstitution, raising the potential for worsening of multifocal systemic inflammation after cessation of therapy. Therefore, patients should be monitored for clinical or laboratory signs of immune reconstitution syndrome (i.e., symptoms associated with cytokine release syndrome or autoimmune sequelae) while on the study and during the 90 day post treatment follow-up
10 period.

12.11.7.4. Tumor lysis syndrome (TLS)

Subjects should be closely monitored for signs and symptoms of TLS both before and after BSBM3 infusion including relevant laboratory tests. To minimize risk of TLS, subjects with elevated uric acid or high tumor burden should receive allopurinol, or an alternative prophylaxis,
15 prior to BSBM3 infusion as indicated. Subjects diagnosed with TLS should be managed according to local guidelines.

12.11.7.5. Gastrointestinal toxicity

Patients should be monitored for GI toxicity and given appropriate supportive care and therapy for symptoms. If a patient has experienced BSBM3 or AL-102-related nausea, vomiting,
20 and/or diarrhea, and it is considered sufficiently severe to warrant the use of prophylactic anti-emetic therapy, then prophylactic therapy may be used in that patient with subsequent treatment. If diarrhea, nausea, vomiting, and/or abdominal pain are observed in patients on BSBM3 alone or in combination with AL-102, clinical evaluation should include a thorough work up of potential infectious etiologies, including systemic infections, prior to the administration of
25 steroids for potential immune-mediated causes of diarrhea or other GI toxicity. Appropriate empiric antibiotic therapy should be considered and started when a localized or systemic infection of the GI tract is suspected as per local institutional guidelines for the treatment of such infections in patients with MM. For patients developing diarrhea in combination Arm B, treatment with loperamide should be initiated at the earliest onset of symptoms. For subjects
30 who cannot tolerate loperamide or do not get adequate relief with maximum doses, standard doses of atropine may be added or used instead of loperamide. Additional antidiarrheal measures, such as octreotide, may be used at the discretion of the investigator or treating physician. Fluid intake should be increased as clinically appropriate. Parenteral hydration should be started if oral hydration is not sufficient. Administration of dexamethasone 8 mg to 10
35 mg daily, followed by tapering over several days, may be considered if colitis is suspected, as in nonclinical models with other GSIs, co-administration of dexamethasone has been shown to decrease the severity of intestinal pathology (Real, 2009; Wei, 2010) . In case of diagnosed or

suspected clinically significant GI bleeding or unexplained drop in hemoglobin, treatment with both drugs should be interrupted to allow for appropriate diagnosis, treatment, and recovery. If GI bleeding is considered related to AL-102, a dose reduction of AL-102 should be considered.

12.12. Additional Treatment Guidance

5 12.12.1. Treatment compliance and accountability

Study drug compliance will be assured by administrations of the study treatment under the supervision of investigator or his/ her designee. Also, it will be verified by determinations of BSBM3 or AL-102 in blood on the days that PK samples are collected.

10 The investigator or designee must maintain an accurate record of the drug receipt logs and Drug Accountability Forms. Drug accountability will be reviewed by the field monitor during site visits and prior to the completion of the study. At study close-out, and, as appropriate during the course of the study, the investigator will return a copy of the completed drug accountability forms to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

15 12.13. Informed Consent Procedure

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent
20 possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

25 Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug
30 can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent
35 and then must be discussed with the subject.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

- 5 A copy of the approved version of all consent forms must be provided to
Novartis/sponsor after IRB/IEC approval.

12.14. Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (Section 12.8.1).

- 10 BSBM3 drug product is formulated for intravenous administration as 50 mg/5 ml liquid in vial (LIVI) concentrate for solution for infusion. The dose for each administration for BSBM3 is based on the patient's actual baseline weight measurement in kilograms on Day 1 (pre-dose). Following the first dose, subsequent doses will only be modified if the patient's weight changes by more than 10% from the Day 1 weight, at which point it will be recalculated using the current weight. AL-102 will be administered as a fixed dose and is provided as a 0.3 mg or 2.0 mg
15 capsule.

A unique medication number is printed on the study medication label.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

20 12.14.1. Handling of study treatment and additional treatment

12.14.1.1. Handling of study treatment

- Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored
25 according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

- 30 Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

- 35 At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the

completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

12.15. Visit schedule and assessments

5 The Assessment Schedules (Table 9) for subjects enrolled in Arm A, and (Table 9-2) for subjects enrolled in Arm B, lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedules (Table 9 or Table 9-2). A visit window of +/- 1 day is permitted to allow scheduling flexibility around holidays or other scheduling conflicts, unless otherwise noted in this protocol.

10 Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

15

TABLE 9 – Assessment Schedule (Arm A)

Visit Name	Category	Baseline/ Screening	Cycle 1						Cycle 2						Subsequent Cycles				End of study treatment (EoT) ¹¹	Follow-up		
			1 ¹	2 ¹	4	8	15	22	1	2	4	8	15	22	1	8	15	22		Last	Safety Follow-up	30 day
Day of cycle		-28 to -1																				
Obtain Informed Consent	D	X																				
Inclusion/exclusion criteria	D	X																				
Demography	D	X																				
Relevant medical history/current medical conditions	D	X																				
Diagnosis and extent of MM	D	X																				
Prior antineoplastic therapy	D	X																				
Physical examination	S	X	X				X		X				X									X
ECOG Performance status	D	X	X									X										X

Visit Name	Category	Baseline/ Screening	Cycle 1				Cycle 2				Subsequent Cycles				End of study treatment (EoT) ¹¹	Follow-up		
Day of cycle		-28 to -1	1 ¹	2 ¹	4	8	15	22	1	2	4	8	15	22	Last	Safety Follow-up		Disease Progression
																30 day	90 day	
Height	D	X																
Weight	D	X	X						X						X			
Vital signs	D	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hematology	D	X	X ²	X ³	X	X	X	X	X	X	X	X	X	X	X			
Chemistry	D	X	X ²	X ³	X	X	X	X	X	X	X	X	X	X	X			
Coagulation	D	X		X ³											X			
Urinalysis (macroscopic)	D		X												X			
Anytime for a suspected cytokine release syndrome, within 5 hours or as soon as possible after the AE																		
Safety cytokines	D	X																
Pregnancy test ⁴	D	X	X ²						X						X	X	X	
Thyroid function	D	X	X						X						X			
Virology ⁵	D	X																
Chest X-ray [for Japan only]	D	X						X ⁶										
Skeletal Survey or CT/MRI for assessment of bony disease ⁷	D	X													X			X

Visit Name	Category	Baseline/ Screening	Cycle 1						Cycle 2						Subsequent Cycles				End of study treatment (EoT) ¹¹	Follow-up		
Day of cycle		-28 to -1	1 ¹	2 ¹	4	8	15	22	1	2	4	8	15	22	1	8	15	22	Last	30 day	90 day	Disease Progression
CT/MRI for assessment of extramedullary disease ⁷	D	X													X				X			X
Serum & Urine M-protein quantification	D	X	X						X						X				X			X
Serum & Urine immunofixation	D	X	X						X						X				X			X
Serum free light chain assay	D	X	X						X						X				X			X
Serum immunoglobulin	D	X	X						X						X				X			X
Disease assessment - bone marrow aspirate ⁸	D	X							X						X				X ⁹			X
Investigator Assessment of Disease response	D								X						X				X			X

Visit Name	Category	Baseline/ Screening	Cycle 1						Cycle 2						Subsequent Cycles				End of study treatment (EoT) ¹¹	Follow-up		
			1 ¹	2 ¹	4	8	15	22	1 ¹	2	4	8	15	22	1	8	15	22		30 day	90 day	Disease Progression
Day of cycle		-28 to -1																				
12-Lead ECG	D	X	X						X						X				X			
Blood sample for PK analysis	D		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Blood sample for ADA analysis	D		X						X						X				X			
Biomarkers - bone marrow aspirate	D	X							X						X				X ⁹			
Biomarkers - blood for immuno-monitoring	D		X	X	X	X			X	X	X											
Biomarkers – blood for soluble immune factors	D		X		X	X			X		X	X			X				X ⁹			
Biomarkers – blood for soluble cytokines	D		X	X	X	X			X	X	X	X										
BSBM3 Administration ¹⁰	D		X			X	X	X	X			X	X	X	X	X	X	X				
Adverse events	D	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Visit Name	Category	Baseline/ Screening	Cycle 1						Cycle 2						Subsequent Cycles				End of study treatment (EoT) ¹¹	Follow-up		
			1 ¹	2 ¹	4	8	15	22	1	2	4	8	15	22	1	8	15	22		Last	Safety Follow-up	30 day
Day of cycle		-28 to -1																				
Concomitant medications	D	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Anti-neoplastic therapies since discontinuation of treatment	D																		X	X	X	X

D = assessment to be recorded in the clinical database or received electronically from a vendor

S = assessment to be recorded in the source documentation only

Table 9-2 Assessment Schedule (Arm B)

Visit Name	Category	Baseline/ Screening	Cycle 1	Cycle 2	Subsequent Cycles	End of study treatment (EoT) ¹²	Follow-up		
							Safety Follow-up	30 day	90 day
Day of cycle		28 -1 to -1	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	Last			
Obtain Informed Consent	D	X							
Inclusion/exclusion criteria	D	X							
Demography	D	X							
Relevant medical history/current medical conditions	D	X							
Diagnosis and extent of MM	D	X							
Prior antineoplastic therapy	D	X							
Physical examination	S	X							
ECOG Performance status	D	X							

Visit Name	Category	Baseline/ Screening	Cycle 1	Cycle 2	Subsequent Cycles	End of study treatment (EoT) ¹²	Follow-up		
							30 day	90 day	Disease Progression
Day of cycle		28 -1 to -1	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	Last			
Height	D	X							
Weight	D	X							
Vital signs	D	X	X	X	X	X	X	X	X
Hematology	D	X	X ³	X	X	X	X	X	X
Chemistry	D	X	X ²	X	X	X	X	X	X
Coagulation	D	X	X ³						
Urinalysis (macroscopic)	D	X							
Safety cytokines	D	X							
Pregnancy test ⁴	D	X ²							
Thyroid function	D	X							
Virology ⁵	D	X							
Chest X-ray [for Japan only]	D	X							
Skeletal Survey or CT/MRI for	D	X							

Visit Name	Category	Baseline/ Screening	Cycle 1	Cycle 2	Subsequent Cycles	End of study treatment (EoT) ¹²	Follow-up		Disease Progression
							30 day Safety Follow-up	90 day Follow-up	
Day of cycle		-28 to -1	1	1	1	Last			
			2	2	2				
assessment of bony disease ⁷			3	3	3				
			4	4	4				
			5	5	5				
			6	6	6				
			7	7	7				
			8	8	8				
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			129	129	129				
			130	130	130				
			131	131	131				

Visit Name	Category	Baseline/ Screening	Cycle 1	Cycle 2	Subsequent Cycles	End of study treatment (EoT) ¹²	Follow-up		
							30 day Safety Follow-up	90 day	Disease Progression
Day of cycle		28 -1 to -1	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	Last			X
CT/MRI for assessment of extramedullary disease ⁷	D	X				X			X
Serum & Urine M-protein quantification	D	X		X	X	X			X
Serum & Urine immunofixation	D	X		X	X	X			X
Serum free light chain assay	D	X		X	X	X			X
Serum immunoglobulin	D	X		X	X	X			X
Disease assessment - bone marrow aspirate ⁸	D	X		X	X	X ⁹			X
Investigator Assessment of	D			X	X	X			X

Visit Name	Category	Baseline/ Screening	Cycle 1	Cycle 2	Subsequent Cycles	End of study treatment (EoT) ¹²	Follow-up		
							30 day Safety Follow-up	90 day	Disease Progression
Day of cycle		28 -1 to -1	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	Last			
Disease response		X	X						
12-Lead ECG	D	X	X			X			X
Blood sample for PK analysis	D	X	X	X	X	X			X
Blood sample for ADA analysis	D	X	X	X	X	X			X
Biomarkers - bone marrow aspirate	D	X	X	X	X	X			X ⁹
Biomarkers - blood for immuno-monitoring	D	X	X	X	X	X			
Biomarkers - blood for soluble immune factors	D	X	X	X	X	X			X ⁹
Biomarkers - blood for	D	X	X	X	X	X			

Visit Name	Category	Baseline/ Screening	Cycle 1	Cycle 2	Subsequent Cycles	End of study treatment (EoT) ¹²	Follow-up		
							30 day Safety Follow-up	90 day Safety Follow-up	Disease Progression
Day of cycle		28 -1 to -1	1 2' 3' 5 8 9 15 16 22 23	1 2 3 5 8 9 15 16 22 23	1 2 3 8 9 15 16 22 23	Last			
soluble cytokines									
BSBM3 Administration ¹⁰	D		X	X	X	X			
AL-102 ^{10, 11} Administration		X	X	X	X				
Adverse events	D	X	X	X	X	X	X	X	
Concomitant medications	D	X	X	X	X	X	X	X	
Anti-neoplastic therapies since discontinuation of treatment	D						X	X	X

12.15.1. Screening

The study IRB/IEC informed consent form must be signed and dated before any screening/baseline procedures are performed; laboratory and radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed within the screening/baseline window.

Subjects will be evaluated against study inclusion and exclusion criteria and safety assessments. For details of assessments, refer to Table 9 and Table 9-2. Screening/Baseline assessments must be repeated if performed outside of the specified screening window.

Submission of a newly obtained bone marrow aspirate is required from all subjects at screening/baseline. For details refer to Section 12.15.3.7.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed, however, the patient ID number will remain the same. All required screening activities must be performed when the patient is re-screened for participation in the study. It is not necessary to repeat the bone marrow aspirate/core biopsy or CT/MRI if performed within 6 weeks of C1D1.

12.15.1.1. Information to be Collected on Screening Failures

A patient who signed an Informed Consent Form but failed to be started on-treatment for any reason will be considered a screen failure. The screening failure reason will be entered on the Screening Phase Disposition eCRF.

The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the patient experienced a SAE during screening/baseline for SAE reporting details) or died (Death eCRF should be completed) or withdrew consent (Withdrawal of consent eCRF should be completed).

12.15.2. Subject demographics/other baseline characteristics

Data to be collected will include general patient demographics, relevant medical history and current medical conditions, diagnosis of multiple myeloma, details of prior anti-neoplastic treatments, prior medication, procedures, significant non-drug therapies and any other assessments that are done for the purpose of determining eligibility for inclusion in the study.

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

12.15.3. Efficacy

Disease classification at baseline and evaluation of response during study treatment rely on blood, urine, and bone marrow assessment, as well as on presence or absence of bony or extramedullary disease. See Table 9 and Table 9-2 for schedule of efficacy assessments.

Disease response will be assessed by the Investigator as detailed in Table 9 and Table 9-2 and as per the International Uniform Response Criteria for MM by the International Myeloma Working Group and will need to be confirmed with two consecutive measurements.

For subjects who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, disease assessments must continue to be performed every 4 weeks until documented disease progression death, lost to follow-up, or withdrawal of consent.

See Section 12.24 for detailed guidelines for efficacy evaluation in MM.

12.15.3.1. Skeletal Survey

A skeletal survey using X-ray, CT or MRI scanning (or other appropriate technique as per institutional practice) must be performed to assess extent of bone disease at Screening (within 28 days prior to first dose of study drug on Day 1 of Cycle 1).

If there is bone disease present at Screening, skeletal survey of affected areas should be performed at Cycle 3 Day 1 (Arm A) or Cycle 3 Day 2 (Arm B), (± 3 days), subsequent cycles as clinically indicated, or to document a response of partial response (PR) or better, or to evaluate disease progression, and at end of treatment. The same imaging modality should be used for post-baseline follow-up when possible.

See Table 9 and Table 9-2.

12.15.3.2. CT/MRI

A CT or MRI scan (or other appropriate technique as per institutional practice) should be performed in subjects with known or suspected extramedullary disease at Screening (within 28 days prior to first dose of study drug on Day 1 of Cycle 1). See Table 9 and Table 9-2.

If disease is documented at screening then CT or MRI scans should be performed at Cycle 3 Day 1, (Arm A) or Cycle 3 Day 2 (Arm B), (± 3 days), subsequent cycles as clinically indicated, or to document a response of PR or better, or to evaluate disease progression, and at end of treatment. The same imaging modality should be used for post-baseline follow-up when possible.

If subjects do not have known or suspected extramedullary disease, imaging with CT/MRI does not need to be performed.

12.15.3.3. Serum and Urine M-Protein

Serum and 24-hour Urine for M-protein must be measured at the following times and as clinically indicated:

- Screening

- At the start of Cycle 1. If screening/baseline samples were obtained within 7 days prior to Cycle 1 Day 1 then samples do not need to be drawn
- On the first day of BSBM3 dosing of Cycles 2-7 (± 3 days)
- On the first day of BSBM3 dosing of Cycle 9, 11, 13 (i.e. every 8 weeks), then every 16 weeks after cycle 13 (± 3 days)
- End of treatment
- Disease progression

12.15.3.4. Serum and Urine Immunofixation

Serum immunofixation must be measured at the following times and as clinically indicated:

- Screening
- At the start of Cycle 1. If screening/baseline samples were obtained within 7 days prior to Cycle 1 Day 1 then samples do not need to be drawn
- On the first day of BSBM3 dosing of Cycles 2-7 (± 3 days)
- On the first day of BSBM3 dosing of Cycle 9, 11, 13 (i.e. every 8 weeks), then every 16 weeks after cycle 13 (± 3 days)
- End of treatment
- Disease progression

12.15.3.5. Serum free light chain assay

Serum free light chain assay will be performed to assess the changes in the immunoglobulin free light chains at the following times and as clinically indicated:

- Screening
- At the start of Cycle 1. If screening/baseline samples were obtained within 7 days prior to Cycle 1 Day 1 then samples do not need to be drawn
- On the first day of BSBM3 dosing of Cycles 2-7 (± 3 days)
- On the first day of BSBM3 dosing of Cycle 9, 11, 13 (i.e. every 8 weeks), then every 16 weeks after cycle 13 (± 3 days)
- End of treatment
- Disease progression

12.15.3.6. Serum Immunoglobulin

Serum Immunoglobulin panel will be performed to assess immunoglobulin levels, and changes in the blood at the following times and as clinically indicated:

- Screening
- 5 • At the start of Cycle 1. If screening/baseline samples were obtained within 7 days prior to Cycle 1 Day 1 then samples do not need to be drawn
- On the first day of BSBM3 dosing of Cycles 2-7 (± 3 days)
- On the first day of BSBM3 dosing of Cycle 9, 11, 13 (i.e. every 8 weeks), then every 16 weeks after cycle 13 (± 3 days)
- 10 • End of treatment
- Disease progression

12.15.3.7. Bone marrow aspirate

A bone marrow aspirate for plasma cell quantification will be collected at the following times and as clinically indicated:

- 15 • Screening (including sample for biomarker assessment)
- On the first day of BSBM3 dosing of Cycle 2 (± 3 days) (including sample for biomarker assessment)
- On the first day of BSBM3 dosing of Cycle 4 pre-dose (± 3 days) (including sample for biomarker assessment)
- 20 • On the first day of BSBM3 dosing of Cycle 7 (± 3 days) (including sample for biomarker assessment)
- At 1 year, on the first day of BSBM3 dosing, Cycle 13 (± 7 days) (including sample for biomarker assessment)
- Disease progression

- 25 • A portion of the bone marrow aspirate sample is required to evaluate biomarkers. If bone marrow aspirate sample is not available or insufficient at screening, a newly obtained bone marrow core biopsy samples should be obtained, if feasible. Refer to the biomarker sample collection plan in for additional details.

12.15.3.8. Investigator Assessment of Disease

- 30 • The assessment of disease response (per the International Uniform Response Criteria for MM, see Section 12.24) will be performed by the Investigator at the following time points and at clinically relevant time points per Investigator discretion:

- On the first day of BSBM3 dosing of Cycles 2-7 (± 3 days)
 - On the first day of BSBM3 dosing of Cycle 9, 11, 13 (i.e. every 8 weeks), then every 16 weeks after cycle 13 (± 3 days)
 - End of treatment
- 5 • At disease progression follow-up

12.15.3.9. Appropriateness of efficacy assessments

The efficacy assessments are a standard approach to measuring and characterizing MM. Additional information is found in Section 12.24.

12.15.4. Safety and tolerability assessments

- 10 Safety will be monitored by assessing physical exam, vital signs, weight, ECOG Performance Status, laboratory evaluations, and cardiac assessment, as well as collecting adverse events at every visit. All safety assessments will be reviewed and/or analyzed locally. ECGs will also be transmitted to a central laboratory and be centrally reviewed by an independent reviewer.

12.15.4.1. Physical examination

- 15 A full physical examination (PE) that evaluates all major organ systems will be performed at screening/baseline and as described in Table 9 and Table 9-2, and may be performed more frequently at the discretion of the treating physician. This should include at least a brief neurological exam. Subsequent PEs should be focused on sites of disease, and
- 20 clinical signs and symptoms.

In some instances, oxygen saturation (SpO₂) will be measured by pulse oximetry for subjects during physical examination as indicated in Table 9 and Table 9-2. The results of SpO₂ will only be recorded in the source documentation.

- 25 Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

12.15.4.2. Vital Signs

- 30 Vital signs (heart rate, blood pressure and temperature) will be obtained at Screening, pre-dose and 4 hours post dose, and at intervals as per institutional guidelines on Day 1, 8, 15, and 22 of each cycle and on all other visit days including EOT. Vital signs should be obtained in the same position, either sitting or supine, as appropriate prior to any blood collection. Please refer to Table 9 and Table 9-2.

12.15.4.3. Height and Weight

Height and weight will be measured at screening/baseline, and weight will be measured on the first day of BSBM3 dosing Day 1 for each subsequent cycle, and at EOT and as clinically indicated. Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Please refer to Table 9 and Table 9-2.

12.15.4.4. Performance Status

ECOG performance status will be documented according to Table 10 and will be collected according to Table 9 and Table 9-2.

Table 10 ECOG Performance Status Scale

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

12.15.4.5. Laboratory evaluations

Laboratory tests will be collected and analyzed by the study site's local laboratory unless otherwise noted even if study drug is being held. More frequent examinations may be performed at the Investigator's discretion if medically indicated; results should be recorded on the Unscheduled Visit eCRFs.

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g., require dose modification and/or interruption of study drug, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded in the AE eCRF. Novartis will be provided with a copy of the laboratory certification and tabulation of the normal ranges for each parameter required. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

Blood samples do not need to be drawn prior to the first dose of study treatment on Cycle 1 Day 1 if screening/baseline samples were obtained within 3 days prior to Cycle 1 Day 1. However, if baseline lab results are borderline for eligibility, abnormal, or otherwise of concern, samples must be drawn prior the first dose of study treatment on Cycle 1 Day 1 regardless of when the baseline samples were drawn, and the results must be reviewed before the patient is treated.

For timing of laboratory assessments, refer to Table 9 and Table 9-2. Laboratory tests are summarized in Table 11.

Table 11 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean Corpuscular Volume (MCV), Platelets, White Blood Cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, and Neutrophils)
Chemistry	Albumin ¹ , Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium ¹ , Sodium, Potassium, Chloride, Magnesium, Phosphate, Creatinine, Direct Bilirubin, Total Bilirubin, Glucose, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Lactate Dehydrogenase (LDH), amylase, lipase If a patient has an abnormal non-fasting glucose value, then a fasting glucose assessment needs to be performed.
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If macroscopic panel is abnormal, microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells).
Coagulation	Partial thromboplastin time (PTT) and one of the following: Prothrombin time (PT) or International normalized ratio (INR). Activated partial thromboplastin time (APTT) is optional.
Cytokines ²	IFN- γ , IL-6, IL-1, TNF- α
Thyroid	Free T3, free T4, TSH
Virology	HIV, HBV, HCV
Pregnancy	Urine b-hcg or serum b-hcg. Women of childbearing potential only
¹ Serum calcium and albumin or ionized calcium are required for disease assessment. ² Samples for the cytokine release panel will be collected at baseline for safety purposes at screening. If a patient has an adverse event suspected to be a cytokine release syndrome, assessment should be performed within 5 hours (or as soon as possible) after occurrence of the adverse event	

12.15.4.6. Cytokine analysis

- 5 Samples for the safety cytokine panel outlined in Table 11 will be collected at screening and on an ad-hoc basis if a subject has an adverse event suspected to be cytokine release syndrome. In such case, this assessment should be performed as soon as possible or within 5 hours after the occurrence of the adverse event. Note that these samples are distinct from those collected for the purpose of PD assessments as indicated in the biomarker sample collection plan (Table 15).
- 10

The samples will be analyzed retrospectively in batches, centrally. The analysis of the samples will be done only for subjects who experienced an adverse event suspected to be a cytokine release syndrome and had follow-up samples collected.

12.15.4.7. Electrocardiogram (ECG)

- 15 A standard 12 lead ECG will be performed at screening, at end of infusion on the first day of each cycle through cycle 6, and at EOT. See Table 12.

Interpretation of the tracing must be made by a qualified physician and documented in the source documentation. Each ECG tracing should be labeled with the study number, subject initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the subject in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page. All eligibility and patient management decisions should be made based on the local reading of the ECG.

- ECGs are to be performed in triplicate, at least 2 minutes apart at the times noted in Table 12 (Arm A) or Table 12-2 (Arm B). However, more frequent ECGs may be performed at the Investigator's discretion, if clinically indicated. Triplicate 12 lead ECGs are to be collected with ECG machines supplied by the ECG vendor. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Table 12 12-lead ECG collection plan (Arm A)

Cycle	Day	Time	ECG Type
Screening	-28 to -1	Anytime	12 Lead, triplicate
1	1	End of-infusion	12 Lead, triplicate
2	1	End of-infusion	12 Lead, triplicate
3	1	End of-infusion	12 Lead, triplicate
4	1	End of-infusion	12 Lead, triplicate
5	1	End of-infusion	12 Lead, triplicate
6	1	End of-infusion	12 Lead, triplicate
EOT	≤14 days from last dose of study drug	Anytime during the EOT visit	12 Lead, triplicate
Unscheduled*	Anytime	Anytime	12 Lead, triplicate

*A PK sample should be collected just after an ECG performed due to an unexpected cardiac signal.

Table 12-2 12-lead ECG collection plan (Arm B)

Cycle	Day	Time	ECG Type
Screening	-28 to -1	Anytime	12 Lead, triplicate
1	1	- Pre-AL-102 dose 1.5 hours post AL-102 dose	12 Lead, triplicate
1	2	- Pre-AL-102 dose 1.5 hours post AL-102 dose - End of BSBM3 infusion	12 Lead, triplicate
2	1	- Pre-AL-102 dose 1.5 hours post AL-102 dose	12 Lead, triplicate
2	2	- Pre-AL-102 dose 1.5 hours post AL-102 dose - End of BSBM3 infusion	12 Lead, triplicate
3	2	End of BSBM3 infusion	12 Lead, triplicate
4	2	End of BSBM3 infusion	12 Lead, triplicate
5	2	End of BSBM3 infusion	12 Lead, triplicate
6	2	End of BSBM3 infusion	12 Lead, triplicate
EOT	≤14 days from last dose of study drug	Anytime during the EOT visit	12 Lead, triplicate
Unscheduled**	Anytime	Anytime	12 Lead, triplicate

*A PK sample should be collected just after an ECG performed due to an unexpected cardiac signal.

ECGs will be transmitted to a central laboratory and be centrally reviewed by an independent reviewer. Any original ECG that was not transmitted to the central laboratory at the time of examination should be forwarded for central review.

- 5 Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.
- 10 All ECGs, including unscheduled triplicate safety ECGs with clinically relevant findings, collected during the study should be transmitted to the central core ECG laboratory for review.

The results of the centrally assessed ECGs are automatically transferred into a clinical database.

12.15.4.8. Pregnancy

- 15 All females of childbearing potential must complete pregnancy testing per Table 9 and Table 9-2.

A serum pregnancy test at screening and on day 1 of each cycle while on treatment and at EOT (Arm A).

A serum pregnancy test must be performed at screening and on day 1 of cycle 1 and 2 on day 2 of each subsequent cycle while on treatment and at EOT (Arm B).

If the screening pregnancy test was performed within 72 hours of the first dose, the test at C1D1 does not need to be repeated.

5 Every month during the safety follow up period, a urine or serum pregnancy test should be performed. This must also be repeated at the end of the safety follow up period. If the patient is not coming to the clinic during the safety follow-up, it can be performed at home or at a local doctor's office, and the results will be communicated to the site staff. These follow-up pregnancy tests will be recorded only in the source documentation, not in the CRF.

10 A positive pregnancy test requires immediate discontinuation of study treatment and discontinuation from study. See Section 12.18.1.4 for pregnancy reporting.

12.15.4.9. Chest X-ray

In some cases, a 2-view chest X-ray will be performed at screening and post dose, Cycle 1 Day 22 (+5 day window allowed, i.e. Day 22 – Day 27) (Arm A) or Cycle 1 Day 23 (+5 day window allowed, i.e. Day 23 – Day 27) (Arm B) to monitor for ILD/pneumonitis.

12.15.4.10. Appropriateness of safety measurements

The inclusion/exclusion criteria, safety assessments, dose modification and adverse event management guidelines in this FIH trial account for both the disease indication in the target patient population and preclinical safety profile of BSBM3.

20 12.15.5. Additional assessments

12.15.5.1. Pharmacokinetics

Serial blood samples will be collected at specified time points as outlined in Table 13 (Arm A) and Table 13-2 (Arm B) to measure serum PK of BSBM3 and sBCMA and Table 13-3 to measure serum AL-102 and sBCMA. Blood samples should be collected from the arm opposite from the study drug infusion, or from another site.

Full PK sampling for BSBM3 and sBCMA during cycle 1 and cycle 2 should be performed on the specified day of dosing.

PK samples will also be collected at the End of Treatment Visit and in the event of a clinically significant AE (such as infusion reaction/anaphylaxis) or if anti-drug antibody is suspected, at which time those samples could be used to measure any relevant biomarkers, to understand the infusion reaction/adverse event better.

The exact date and clock times of study drug administration and blood sample collection will be recorded on the appropriate eCRF. Any sampling issues should be noted on the eCRF and on appropriate source documentation.

Residual samples used for PK and/ or IG analysis may also be used for exploratory PK or PK/PD analyses. This could include using leftover samples for protein binding analysis, metabolite profiling, or exploratory biomarker analysis, if there is sufficient sample remaining.

Table 13 Pharmacokinetic blood collection log for BSBM3 and sBCMA

Cycle	Day	Scheduled Time Point (h) ^b
1	1	Pre-dose
1	1	5 min post-dose (post end of infusion)
1	1	1h post-dose (± 5 min)
1	1	4h post-dose (± 15 min)
1	1	8h post-dose (± 15 min)
1	2	24h post-dose (± 2 h) ^c
1	2	5 min post-dose (post end of infusion)*
1	4	72h post-dose (± 8 h)
1	8	Pre-dose
1	15	5 min post-dose
1	22	Pre-dose
2	1	Pre-dose
2	1	5 min post-dose
2	1	1h post-dose (± 5 min)
2	1	4h post-dose (± 15 min)
2	1	8h post-dose (± 15 min)
2	2	24h post-dose (± 2 h)
2	4	72h post-dose (± 8 h)
2	8	Pre-dose
2	15	5 min post-dose
2	22	Pre-dose
3	1	Pre-dose
4	1	Pre-dose
5	1	Pre-dose
6	1	Pre-dose
EOT ^a		Anytime
Unscheduled		Anytime
^a A PK sample collection will occur at cycle 6 or EOT, whichever occurs first ^b sBCMA will be measured for each sample collection time point described in the Table 13 ^c Pre-dose at priming dose *Priming dose only		

5 Table 13-2 Pharmacokinetic blood collection log for BSBM3 and sBCMA (Arm B)

Cycle	Day	Scheduled Time Point (h) ^b
1	2	Pre-dose
1	2	5 min post-dose (post end of infusion)
1	2	1h post-dose (± 5 min)
1	2	4h post-dose (± 15 min)

Cycle	Day	Scheduled Time Point (h) ^b
1	2	8h post-dose (± 15 min)
1	3	24h post-dose (± 2 h) ^c
1	3	5 min post-dose (post end of infusion)*
1	5	72h post-dose (± 8 h)
1	9	Pre-dose
1	16	5 min post-dose
1	23	Pre-dose
2	2	Pre-dose
2	2	5 min post-dose
2	2	1h post-dose (± 5 min)
2	2	4h post-dose (± 15 min)
2	2	8h post-dose (± 15 min)
2	5	72h post-dose (± 8 h)
2	9	Pre-dose
2	16	5 min post-dose
2	23	Pre-dose
3	2	Pre-dose
4	2	Pre-dose
5	2	Pre-dose
6	2	Pre-dose
EOT ^a		Anytime
Unscheduled		Anytime
^a A PK sample collection will occur at cycle 6 or EOT, whichever occurs first ^b Shed BCMA will be measured for each sample collection time point described in the Table 13-2 and will be described in the CBSBM3A12101 Laboratory Manual ^c Pre-dose at priming dose *Priming dose only		

Serial blood samples will be collected at specified time points as outlined in Table 13-3 to measure plasma PK of AL-102 and its active metabolite and serum sBCMA.

5 Full PK sampling for AL-102, its active metabolite, and sBCMA during cycle 1 and cycle 2 should be performed on the specified day of dosing. As inhibition of the shedding of BCMA from myeloma cells by administration of AL-102 may lead to reduction of BCMA-mediated clearance of BSBM3 thus sBCMA will be measured to assess impact of AL-102 on shedding and BCMA-mediated clearance of BSBM3.

10 The exact date and clock times of study drug administration and blood sample collection will be recorded on the appropriate eCRF. Any sampling issues should be noted on the eCRF and on appropriate source documentation.

Residual samples used for PK analysis may also be used for exploratory PK or PK/PD analyses. This could include using leftover samples metabolite profiling, or exploratory biomarker analysis, if there is sufficient sample remaining.

Table 13-3 Pharmacokinetic blood collection log for AL-102, its metabolite and sBCMA (Arm B)

Cycle	Day	Scheduled Time Point (h) ^{a, b}
1	1	Pre-dose
1	1	1h post-dose (± 5 min)
1	1	1.5h post-dose (± 15 min)
1	1	2h post-dose (± 15 min)
1	1	4h post-dose (± 15 min)
1	1	8h post dose (± 15 min)
1	2	Pre-dose
1	2	1h post-dose (± 5 min)
1	2	1.5h post-dose (± 15 min)
1	2	2h post-dose (± 15 min)
1	2	4h post-dose (± 15 min)
1	2	8h post dose (± 15 min)
1	3	24h post-dose (± 8 h)
1	5	72h post-dose (± 8 h)
1	9	Pre-dose
2	1	1h post-dose (± 5 min)
2	1	1.5h post-dose (± 15 min)
2	1	2h post-dose (± 15 min)
2	1	4h post-dose (± 15 min)
2	1	8h post dose (± 15 min)
2	2	Pre-dose
2	2	1h post-dose (± 5 min)
2	2	1.5h post-dose (± 15 min)
2	2	2h post-dose (± 15 min)
2	2	4h post-dose (± 15 min)
2	2	8h post dose (± 15 min)
2	5	72h post-dose (± 8 h)
2	9	Pre-dose
EOT		Anytime
Unscheduled		Anytime
^a All time points are relative to AL-102 dosing		
^b sBCMA will be measured for each sample collection time point described in the Table 13-3		

12.15.5.1.1. Analytical method for PK samples

Bioanalysis for pharmacokinetic studies will employ validated ELISA assays to measure BSBM3 in serum and validated liquid chromatography-mass spectrometry (LC-MS/MS) assays to measure AL-102 and its metabolite in EDTA plasma.

Any results below the lower limit of quantification (LLOQ) will be reported as BLQ (below the limit of quantitation). Any missing samples will be labeled accordingly.

12.15.5.2. Immunogenicity assessments

Bloods samples will be collected at specified time points as outlined in **Table 14 (Arm A) or Table 14-2 (Arm B)** to measure BSBM3 anti-drug antibodies (ADA). Blood samples

should be collected from the arm opposite from the study drug infusion, or from another site. ADA samples will also be collected at the End of Treatment Visit and in the event of a clinically significant AE (such as infusion reaction/anaphylaxis) or if anti-drug antibody is suspected, at which time those samples could be used to measure any relevant biomarkers, to understand the infusion reaction/adverse event better.

The exact date and clock times of study drug administration and blood sample collection will be recorded on the appropriate eCRF. Any sampling issues should be noted on the eCRF and on appropriate source documentation.

Residual serum samples ADA analysis may also be used for exploratory PK and/or PD analyses.

Table 14 Blood collection log for ADA in Arm A

Cycle	Study day	Scheduled time point (Sampling window)	Analytes
1	1	Pre-dose ^b (0 h)	ADA ^a
2	1	Pre-dose ^b of cycle 2 (0 h) / 672h (± 8h) post end of infusion dose cycle 1	ADA ^a
3	1	Pre-dose ^b of cycle 3 (0 hr) / 672h (± 8h) post end of infusion dose cycle 2	ADA ^a
4	1	Pre-dose ^b of cycle 4 (0 h) / 672h (± 8h) post end of infusion dose cycle 3	ADA ^a
5	1	Pre-dose ^b of cycle 5 (0 h) / 672h (± 8h) post end of infusion dose cycle 4	ADA ^a
6	1	Pre-dose ^b of cycle 6 (0 h) / 672h (± 8h) post end of infusion dose cycle 5	ADA ^a
EOT ^c		Anytime	ADA ^a
Unscheduled		Anytime	ADA ^a
Blood samples are to be collected from the arm opposite from infusion site, or alternatively, infusion site will need to be flushed with 10 mL of saline. ^a Immunogenicity (IG) (Anti-Drug [BSBM3] Antibody): blood samples to be collected for anti-drug antibody together with BSBM3 PK samples ^b Pre-dose blood samples should be collected prior to start of infusion of treatment ^c A PK sample collection will occur at cycle 6 or EOT, whichever occurs first			

Table 14-2 Blood collection log for ADA in Arm B

Cycle	Study day	Scheduled time point (Sampling window) ^d	Analytes
1	2	Pre-dose ^b (0 h)	ADA ^a
2	2	Pre-dose ^b of cycle 2 (0 h) / 672h (± 8h) post end of infusion dose cycle 1	ADA ^a
3	2	Pre-dose ^b of cycle 3 (0 hr) / 672h (± 8h) post end of infusion dose cycle 2	ADA ^a
4	2	Pre-dose ^b of cycle 4 (0 h) / 672h (± 8h) post end of infusion dose cycle 3	ADA ^a
5	2	Pre-dose ^b of cycle 5 (0 h) / 672h (± 8h) post end of infusion dose cycle 4	ADA ^a
6	2	Pre-dose ^b of cycle 6 (0 h) / 672h (± 8h) post end of infusion dose cycle 5	ADA ^a

Cycle	Study day	Scheduled time point (Sampling window) ^d	Analytes
EOT ^c		Anytime	ADA ^a
Unscheduled		Anytime	ADA ^a
Blood samples are to be collected from the arm opposite from infusion site, or alternatively, infusion site will need to be flushed with 10 mL of saline. ^a Immunogenicity (IG) (Anti-Drug [BSBM3] Antibody): blood samples to be collected for anti-drug antibody together with BSBM3PK samples ^b Pre-dose blood samples should be collected prior to start of infusion of treatment ^c A PK sample collection will occur at cycle 6 or EOT, whichever occurs first ^dTiming of collection is relative to BSBM3infusion			

12.15.5.2.1. Analytical method for ADA samples

The assay to quantify and assess the ADA against BSBM3 will be in serum using a validated homogeneous ELISA.

- 5 Any results below the lower limit of quantification (LLOQ) will be reported as BLQ (below the limit of quantitation). Any missing samples will be labeled accordingly.

12.15.5.3. Biomarkers

- 10 Biomarker analyses will be used to investigate the effect of single agent BSBM3 (Arm A), and BSBM3 in combination with AL-102 (Arm B) at the molecular and cellular level as well as to determine how changes in the markers may relate to exposure and clinical outcomes. In addition, potential predictive markers of efficacy, as well as mechanisms of resistance to BSBM3 as a single agent will also be explored.

- 15 While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (e.g. inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc.). Therefore, depending on the results obtained during the study, sample collection or analysis may be omitted at the discretion of the Novartis.

- 20 The sample collection information must be entered on the appropriate sample collection eCRF pages and requisition forms. Detailed instructions for the collection, processing, and shipment of biomarker samples are outlined in the laboratory manual for the study. Samples should be collected at the visit/time points defined in the biomarker table; Table 15 (Arm A) or Table 15-2 (Arm B).

- 25 **Table 15** Biomarker sample collection plan (Arm A)

Sample Type	Visit/Time point	Approx. Volume	Marker	Purpose
Bone Marrow Aspirate (1st Pull) ^{*/**}	Baseline/ screening C2D1 C4D1 C7D1 C13D1 Disease progression/ End of treatment ^{***}	2-2.5 mL	Phenotypic characterization of malignant cells (e.g. BCMA, CD19, CD138, CD38, CD56, CD45, BCMA, CD27, CD28, CD20, CD117) And T cells: (e.g. CD3, CD4, CD8, FoxP3, Tim-3, PD-1, Lag-3, Ki67, CD27)	Immunophenotyping Determination of mBCMA expression on myeloma cells.
Bone Marrow Aspirate (2nd Pull) [*]	Baseline/ screening C2D1 C4D1 C7D1 C13D1 Disease progression/ End of treatment ^{***}	2-2.5mL	IgH rearrangements and translocations	MRD determination and monitoring
Bone Marrow Aspirate (3rd Pull) [*]	Baseline/ screening C2D1 Disease progression/ End of treatment ^{***}	2-2.5mL	Nucleic acid based analyses of cancer and immune related genes (e.g. BCMA)	Assess potential predictive markers of response & mechanisms of resistance.
Blood for Immunomonitoring	C1D1 pre-dose C1D2 (24 hours post) C1D4 (72 hours post) C1D8 (pre-dose) C2D1 (pre-dose) C2D2 (24 hours) C2D4 (72 hours post) C2D8 (pre-dose)	10 mL	Phenotypic characterization of circulating immune cells (e.g. CD45, CD3, CD4, CD8)	Pharmacodynamic effect
Blood for soluble immune factors	C1D1 pre-dose C1D4 (72 hours post) C1D8 (pre-dose) C2D1 (pre-dose) C2D4 (72 hours post) C2D8 (pre-dose) C4D1 (pre-dose) C7D1 (pre-dose) C13D1 (pre-dose)	3 mL	Soluble Immune factors (e.g. sBCMA)	Assess potential predictors of efficacy

Sample Type	Visit/Time point	Approx. Volume	Marker	Purpose
	Disease progression/End of treatment***			
Blood for soluble cytokines	C1D1 pre-dose C1D1 (4 hours post) C1D1 (8 hours post) C1D2 (24 hours post) C1D4 (72 hours post) C1D8 (pre-dose) C2D1 (pre-dose) C2D1 (4 hours post) C2D1 (8 hours post) C2D2 (24 hours post) C2D4 (72 hours post) C2D8 (pre-dose)	3 mL	Cytokine analysis (e.g. IFN- γ , IL-2, IL-4, IL-6, IL-8, IL-10, IL-15, TNF- α)	Assessment of cytokines
*Bone marrow aspirate should be collected in order of priority as outlined in the table above **Bone marrow aspirate collected for biomarker assessment will be collected after aspirate collection for disease assessment. If cellular content is available a portion of the aspirate collection for disease assessment may be for biomarker assessment. *** Sample to be collected upon disease progression, if this date is > 15 days from the EoT visit an additional sample at EoT visit is requested.				

Table 15-2 Biomarker sample collection plan (Arm B)

Sample Type	Visit/Time point	Approx. Volume	Marker	Purpose
Bone Marrow Aspirate (1st Pull)*/**	Baseline/ screening C2D2 C4D2 C7D2 C13D2 Disease progression/ End of treatment***	2-2.5 mL	Phenotypic characterization of malignant cells (e.g. BCMA, CD19, CD138, CD38, CD56, CD45, BCMA, CD27, CD28, CD20, CD117) And T cells: (e.g. CD3, CD4, CD8, FoxP3, Tim-3, PD-1, Lag-3, Ki67, CD27)	Immunophenotyping Determination of mBCMA expression on myeloma cells.

Sample Type	Visit/Time point	Approx. Volume	Marker	Purpose
Bone Marrow Aspirate (2nd Pull)*	Baseline/ screening C2D2 C4D2 C7D2 C13D2 Disease progression/ End of treatment***	2-2.5mL	IgH rearrangements and translocations	MRD determination and monitoring
Bone Marrow Aspirate (3rd Pull)*	Baseline/ screening C2D2 Disease progression/ End of treatment***	2-2.5mL	Nucleic acid based analyses of cancer and immune related genes (e.g. BCMA)	Assess potential predictive markers of response & mechanisms of resistance.
Blood for Immunomonitoring	C1D1 pre-dose C1D2 pre-dose C1D3 (24 hours post) C1D5 (72 hours post) C1D9 (pre-dose) C2D1 (pre-dose) C2D2 (pre-dose) C2D5 (72 hours post) C2D9 (pre-dose)	10 mL	Phenotypic characterization of circulating immune cells (e.g. CD45, CD3, CD4, CD8)	Pharmacodynamic effect
Blood for soluble immune factors	C1D1 (pre-dose) C1D1 (4 hours post) C1D1 (8 hours post) C1D2 (pre-dose) C1D5 (72 hours post) C1D9 (pre-dose) C2D1 (pre-dose) C2D1 (4 hours post) C2D1 (8 hours post) C2D2 (pre-dose) C2D5 (72 hours post) C2D9 (pre-dose) C4D2 (pre-dose) C7D2 (pre-dose) C13D2 (pre-dose) Disease progression/End of treatment***	3 mL	Soluble Immune factors (e.g. sBCMA)	Assess potential predictors of efficacy

Sample Type	Visit/Time point	Approx. Volume	Marker	Purpose
Blood for soluble cytokines	C1D1 pre-dose C1D1 (8 hours post) C1D2 pre-dose C1D2 (4 hours post) C1D2 (8 hours post) C1D3 (24 hours post) C1D5 (72 hours post) C1D9 (pre-dose) C2D1 (pre-dose) C2D2 (pre-dose) C2D2 (4 hours post) C2D2 (8 hours post) C2D5 (72 hours post) C2D9 (pre-dose)	3 mL	Cytokine analysis (e.g. IFN- γ , IL-2, IL-4, IL-6, IL-8, IL-10, IL-15, TNF- α)	Assessment of cytokines
*Bone marrow aspirate should be collected in order of priority as outlined in the table above **Bone marrow aspirate collected for biomarker assessment will be collected after aspirate collection for disease assessment. If cellular content is available a portion of the aspirate collection for disease assessment may be for biomarker assessment. *** Sample to be collected upon disease progression, if this date is > 15 days from the EoT visit an additional sample at EoT visit is requested.				

Tissue collection

Bone marrow aspirate samples are required and will be collected from all subjects per the schedule outlined in Table 15 (Arm A) or Table 15-2 (Arm B) above. In the event that an adequate bone marrow aspirate is not obtained at screening (e.g. dry tap or low yield) a newly collected bone marrow core biopsy sample, if feasible, must be provided for biomarker studies at screening.

Phenotypic characterization of immune and malignant cells as well as nucleic acid-based analyses may be conducted on bone marrow samples to assess disease status, characterize pharmacodynamic effect, and assess potential mechanisms of response and resistance to BSBM3 treatment.

Blood collection

Collection of peripheral blood for PD assessments will allow the assessment of BSBM3 target and pathway modulation by measuring soluble immune factors and cytokines (e.g. sBCMA, IFN- γ , IL-2, IL-4, IL-6, IL-8, IL-10, IL-15, TNF- α) and for the assessment of markers of activation in circulating immune cells. Collection of blood samples for PD effects is mandatory for all subjects.

Additional exploratory analysis

During the study, in addition to the biomarkers specified above, exploratory biomarker research may be conducted on any remaining biomarker and/or PK samples. These studies would extend the search for other potential relevant biomarkers for BSBM3 and/or BSBM3 effect and/or safety. This may also include the development of ways to detect, monitor or treat cancer. These additional investigations would be dependent upon clinical outcome, reagent and sample availability.

Use of residual biological samples

If the subject agrees, the biomarker samples that remain after analysis is completed (bone marrow aspirate / core biopsy, blood, plasma, and serum) may be kept for up to 15 years to be used for additional studies related to BSBM3 or cancer, including research to help develop ways to detect, monitor or treat cancer. A decision to perform such exploratory biomarker research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as assay availability.

12.16. Study discontinuation and completion

12.16.1. Discontinuation

12.16.1.1. Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Any protocol deviation or situation in which continued study participation might result in a safety risk to the subject or significantly impact the integrity of the trial results
- Emergence of adverse events that meet the discontinuation criteria as per Table 6
- If a patient requires a dose delay for > 21 consecutive days due to treatment-related toxicity, unless, documented evidence of clinical benefit from study treatment and, in the opinion of the Investigator, it is in the patient's best interest

to continue treatment, and no safety concerns are present, and after documented discussion with Novartis.

- Any laboratory abnormalities that in the judgment of the investigator, prevents the subject from continuing participation in the study

5 If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they
10 withdraw their consent (see withdraw of informed consent section). Where possible, they should return for the assessments indicated in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

15 If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- 20
- new / concomitant treatments
 - adverse events/Serious Adverse Events

For subjects who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed as clinically indicated until documented disease progression, death,
25 lost to follow-up, or withdrawal of consent.

12.16.1.1.1. Replacement policy

Subjects will not be replaced on study. All treated subjects will contribute to the final analyses. However, during dose escalation, if a subject is considered as non-evaluable for the Dose Determining Set (DDS), enrollment of a new subject to the current cohort may be
30 considered in order to support the benefit-risk assessment for dose-escalation.

12.17. Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and

- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

- 5 Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

- 10 All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

- 15 For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

- 20 For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

12.17.1.1. Lost to Follow-Up

- 25 For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

12.17.1.2. Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- 30
- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
 - Decision based on recommendations from applicable board(s) after review of safety and efficacy data

- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional
5 procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

12.17.2. Study completion and post-study treatment

12.17.2.1. End of Study

10 The end of study will be when at least 80% of the subjects in the expansion part have completed the follow-up for disease progression or discontinued the study for any reason, and all subjects have completed the 90 day safety follow-up.

The disease follow-up evaluations might not be completed in case Novartis decides to stop enrollment prematurely. In such cases, end of study will be when the treatment period and
15 the safety follow-up have been completed for all subjects.

12.17.2.1.1. Safety follow-up

All subjects receiving single agent BSBM3 or BSBM3 in combination with AL-102 must have safety evaluations until 90 days after the last dose of study treatment.

Concomitant medications will be collected until the 90-day safety follow-up has been
20 completed or the start of a new antineoplastic therapy, whichever occurs first.

For female subjects of child bearing potential, pregnancy tests will be performed monthly as outlined in Section 12.15.4.8.

Follow-up with study subjects will occur at 30 days and 90 days after the last dose of study treatment and can be done by telephone call or visit.

25 Data collected during the follow-up period including adverse events, concomitant medication, results of pregnancy tests (if applicable), and antineoplastic therapies initiated since discontinuation of study treatment, should be added to the appropriate CRF pages.

12.17.2.1.2. Disease progression follow-up

Subjects who discontinue study treatment for any reason other than death, disease
30 progression per IMWG while on treatment, clinical deterioration, lost to follow-up, consent withdrawal, study termination, or initiation of subsequent anti-cancer treatment, also should return for disease assessments every 4 weeks until documented disease progression, death, lost to follow-up, or withdrawal of consent.

If subjects refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine if the patient had disease progression.

12.18. Safety monitoring and reporting

5 12.18.1. Definition of adverse events and reporting requirements

12.18.1.1. Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information.

The severity grade (CTCAE Grade 1-5);

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

1. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
2. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
3. whether it constitutes a SAE and which seriousness criteria have been met
4. action taken regarding with study treatment

5. All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- 5 • Drug interrupted/withdrawn

6. its outcome (i.e. recovery status or whether it was fatal)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the
10 CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

15 Adverse event monitoring should be continued for at least 90 days following the last dose of study treatment. If after 30 days post last dose of study treatment, a new post-treatment antineoplastic therapy is initiated, only AEs suspected to be related to study treatment will be collected in the Adverse Event CRF.

Once an adverse event is detected, it must be followed until its resolution or until it is
20 judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented per IMWG, should not be reported as a serious adverse event.

25 Adverse events separate from the progression of malignancy (i.e. deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Information about adverse drug reactions for the investigational drug can be found in the
30 Investigator's Brochures (IBs).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms

- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease.

12.18.1.2. Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
 - social reasons and respite care in the absence of any deterioration in the subject's general condition
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 - is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as “medically significant”. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

12.18.1.3. SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 90 days after last dose must be reported to Novartis safety within 24 hours of learning of its occurrence.

If after 30 days post last dose of study treatment, a subject starts a post-treatment antineoplastic therapy, then only SAEs suspected to be related to study treatment will be reported.

SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Any SAEs experienced after the completion of the safety evaluation follow-up period (as described above) should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event. If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 90 day follow-up period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

12.18.1.4. Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

After the mother has provided consent, the newborn will be followed-up for 12 months.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship of the study treatment to any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

12.18.1.5. Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 16 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

12.18.2. Additional Safety Monitoring

12.18.2.1. Data Monitoring Committee

A data monitoring board will not be used for this study. This is an open-label, Phase I study and Novartis will have access to the Safety Data on a regular basis. Novartis will host investigator teleconferences on a regular basis during the study. Further, Novartis and the investigators will meet at the end of each treatment cohort to discuss and evaluate all of the gathered safety data. At the dose escalation teleconference the clinical course (safety information including both DLTs and all CTCAE Grade 2 or higher toxicity data during the DLT evaluation period, and available PK data) for each subject in the current dose cohort will be described in detail. Updated safety data on other ongoing subjects, including data in later cycles, will be discussed as well.

12.19. Data collection and database management

12.19.1. Data collection

Designated investigator staff will enter the data required by the protocol into the electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

5 After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Dose escalation decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study, including safety information, PK, and available PD and preliminary anti-cancer activity data. In particular, the following core data are required to be reviewed for each subject in each cohort to be discussed in the dose escalation meeting, prior to deciding the next steps:

10

Safety: AEs, SAEs, DLTs.

Laboratory parameters: hematological parameters (hemoglobin, platelets, WBC, Neutrophils), renal function tests (BUN/urea, creatinine, sodium, potassium), liver function tests (AST, ALT, total bilirubin, ALP).

15 Dosing information collected during the DLT observation period, prior and concomitant medications, demographics and diagnosis and extent of cancer (which are relevant to inclusion/exclusion criteria), date of visit and end of treatment phase disposition (if end of treatment has already occurred for a subject who is in a cohort to be discussed in the dose escalation meeting).

20 All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation, and verification.

12.19.2. Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

25

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

30

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician.

Any changes to the database after that time can only be made after written agreement by Novartis development management.

12.19.3. Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12.20. Data analysis and statistical methods

Data from participating centers in this protocol will be combined, so that an adequate number of subjects will be available for analysis. Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, and efficacy, safety, pharmacokinetic and pharmacodynamics measurements.

Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Study data will be analyzed and reported in a primary CSR based on all subjects' data up to the time when all subjects have completed at least six cycles of study treatment or discontinued treatment. Any additional data for subjects continuing to receive study treatment past the data cutoff date for the primary CSR, as allowed by the protocol, will be reported at completion of the study in a final CSR.

Subjects treated with the same dosing regimen (dose and dosing schedule) of BSBM3 or dose combination will be pooled into a single treatment group (including subjects from dose escalation and dose expansion parts) All summaries, listings, figures and analyses will be performed by treatment groups (unless otherwise specified). Arms to be analyzed are:

- Arm A: Single Agent BSBM3
- Arm B: Combination BSBM3 + AL-102

Screen failure subjects, as described in Section 12.15.1.1, and the reasons for not starting the study treatment will be reported in a listing, but will not be included in any analyses.

- Dose escalation decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study, including safety information, PK, and available PD and preliminary anti-cancer activity data. In particular, the following core data are required to be reviewed for each subject in each cohort to be discussed in the dose escalation meeting, prior to deciding the next steps:

Safety: AEs, SAEs, DLTs.

- Laboratory parameters: hematological parameters (hemoglobin, platelets, WBC, Neutrophils), renal function tests (BUN/urea, creatinine, sodium, potassium), liver function tests (AST, ALT, total bilirubin, ALP).

- Dosing information collected during the DLT observation period, prior and concomitant medications, demographics and diagnosis and extent of cancer (which are relevant to inclusion/exclusion criteria), date of visit and end of treatment phase disposition (if end of treatment has already occurred for a subject who is in a cohort to be discussed in the dose escalation meeting).

Details of the statistical analysis and data reporting will be provided in the Statistical Analysis Plan (SAP).

- Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.20.1. Analysis sets

The Full Analysis Set (FAS) and Safety Set (SS) comprise all subjects who received at least one dose of any study drug (i.e. at least one dose of BSBM3 or AL-102). Subjects will be

analyzed according to the study treatment received, defined as the treatment most frequently taken between Study Day 1 and the end of the DLT evaluation period (i.e. the first 28 days of dosing), the onset of a DLT or treatment discontinuation, whichever occurs first. In case of a priming dose being used, the study treatment received is defined using the combination of
 5 priming dose and the treatment most frequently taken after priming dose (i.e. between Study Day 8 and Day 28).

The Dose-Determining Set (DDS) includes all FAS subjects who met the minimum exposure criterion and have sufficient safety evaluations (as determined by Novartis and Investigator), or experienced a dose limiting toxicity (DLT) during the DLT-evaluation period (i.e.
 10 the first 28 days of dosing). A subject has met the minimum exposure criterion if she/he received at least 75% of dosing as per the planned received regimen (i.e. at least 3 doses of BSBM3 for Q1W Schedule or 6 doses of AL-102 for 2 days on/ 5 days off schedule with a minimum of at least 1 dose of AL-102 per BSBM3 administration) during the DLT evaluation period).

15 The Pharmacokinetic analysis set (PAS) for BSBM3 and sBCMA in Arm A includes all subjects who provide an evaluable PK profile. A profile is considered evaluable if all of the following conditions are satisfied:

- Subject receives one of the planned treatments
- Subject provides at least one primary PK parameter

20 The Pharmacokinetic analysis set (PAS) for BSBM3, sBCMA, AL-102 and its metabolite in Arm B includes all subjects who provide an evaluable PK profile. A profile is considered evaluable if all of the following conditions are satisfied:

- Subject receives one of the planned treatments
- Subject provides at least one primary PK parameter
- 25 • Subject does not vomit within 4 hours after dosing of AL-102

12.20.2. Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by arm and treatment group for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous
 30 data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by arm and treatment group.

12.20.3. Treatments

The Safety set will be used for the analyses below.

The duration of exposure in weeks to study drug will be summarized by means of descriptive statistics using the safety set.

The number of subjects with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons for dose adjustments will be summarized by arm and

5 treatment group. All dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by arm and treatment group.

12.20.4. Analysis of the primary endpoint(s)

10 The primary objective is to characterize the safety and tolerability of single agent BSBM3, and BSBM3 in combination with AL-102, and identify a recommended dose and/or regimen which will be used in expansion.

12.20.4.1. Safety Endpoints

12.20.4.1.1. Definition of primary endpoints(s)

The primary endpoints are described in Table 17.

15 **Table 17** Primary endpoints

Objective	Primary endpoint
Safety	Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs, ECGs, and CRS/immune-mediated reactions
Tolerability	Dose interruptions, reductions, and dose intensity
Identification of recommended dose	Incidence of dose limiting toxicities (DLTs) in Cycle 1

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as clinically relevant, occurring ≤ 28 days following the first administration of study treatment as defined in Section 12.11.3, Table 5.1.

12.20.4.1.2. Statistical hypothesis, model, and method of analysis

20 For all safety analyses, except the DLT analyses, the safety set will be used. All listings and tables will be presented by arm and treatment group.

The overall observation period will be divided into three mutually exclusive segments:

Pre-treatment period

- From day of subject's first informed consent to the day before first administration of study drug

On-treatment period

- From date of first administration of any study drug to 30 days after date of last actual administration of any study drug (including start and stop date).

Post-treatment period

- Starting at 31 after last administration of any study drug.

Safety summaries will primarily be based on all data from the on-treatment period.

Following last administration of any study drug, adverse events (including serious adverse events), and new antineoplastic therapies are collected for a period of 90 days. Following start of new antineoplastic therapy only treatment related adverse events will be collected. Select summaries of related adverse events will be produced for the combined on-treatment and post-treatment periods.

Dose-limiting toxicities

Estimation of the MTD of the treatment will be based upon the estimation of the probability of DLT in Cycle 1 (i.e. the first 28 days) for subjects in the DDS. A recommended dose below the MTD may be identified based on other safety, clinical, PK, and PD data.

Bayesian adaptive approach

Bayesian adaptive BLRM for single agent and BHLRM for combination guided by the EWOC criteria will be used to make dose recommendations and estimate the appropriate MTD during the dose escalation part of the study. The BLRM/BHLRM will be fit on the dose-limiting toxicity data (i.e. absence or presence of DLT) during the DLT window accumulated throughout the dose escalation to model the dose-toxicity relationship.

In case of escalating with priming dose or exploring other dosing schedules, a separate BHLRM analyzing Cycle 1 dose DLT data (i.e. first 28 days) will be used to guide the dose escalation by the EWOC principle. A full description including parameter specification, operating characteristics and hypothetical dose scenarios of the BHLRM will be given in a stand alone document(s), prior to the first patient is treated on cohort with priming dose or alternative dosing schedule(s).

BSBM3 single agent BLRM (Arm A)

The Arm A dose escalation will be guided by a 2-parameter BLRM based on the first Cycle DLT data (i.e. first 28 dyas) of the study treatment. This model estimates the relationship between dose and the probability of a subject experiencing a DLT treated with single agent BSBM3 on a QW schedule. A weakly informative mixture prior of the model was derived based on pre-clinical data and a robust higher toxicity component.

Specifications of the model priors are described throughout the specification.

Combination BHLRM (Arm B)

- The Arm B dose escalation will be guided by a meta-analytic-combined (MAC) BHLRM based on the first Cycle DLT data of the study treatment. The model will integrate both single-agent and combination toxicity parts. Both historical data and concurrent data are incorporated into the model. For different regimens, a plausible between-cohorts heterogeneity will be assumed, allowing for non-exchangeability across trial parameters. A full description of the application of the BHLRM with MAC including parameter specification and hypothetical dose scenarios described throughout.

Assessment of subject risk

- After each cohort of subjects in dose escalation, the posterior distribution for the risk of DLT for new subjects at doses of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

Under-dosing:	[0 , 0.16)
Targeted toxicity:	[0.16 , 0.33)
Excessive toxicity:	[0.33 , 1]

The Escalation with Overdose Control (EWOC) Principle

Dosing decisions are guided by the BLRM with EWOC principle. A dose may only be used for newly enrolled subjects if the risk of excessive toxicity at that dose is less than 25%.

Starting dose

BSBM3 single agent dose escalation

- The starting dose is 3 mcg/kg BSBM3 QW. For this dose the prior risk of excessive toxicity is 5.6%, which satisfies the EWOC criterion. A full assessment of the prior risk to subjects is given in Section 12.25.

BSBM3 in combination with AL-102 dose escalation

- The starting dose of BSBM3 in the combination therapy will be at least one dose level lower than the highest tolerated safe dose tested (i.e. satisfying EWOC principle based on BLRM model) in the single agent dose escalation part. The initial dose and schedule for AL-102 will be 2 mg on a 2 days on / 5 days off schedule (BIW) with the administration of AL-102 one day before and on the day of BSBM3 administration every week until study discontinuation.

Reporting

Bayesian analyses will be based on the DDS. DLTs will be listed, and their incidence summarized by primary system organ class and worst grade (CTCAE version 5.0), using the DDS.

Adverse events

5 All information obtained on adverse events will be displayed by treatment group and subject.

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of study treatment but increased in severity based on preferred term) will be summarized in the following
10 ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term

Separate summaries will be provided for study medication related adverse events,
15 death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Summary tables for AEs will include only AEs that started or worsened during the on-
20 treatment period, the treatment-emergent AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, and relationship to study treatment.

Serious adverse events, non-serious adverse events during the on-treatment period will
25 be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

30 Vital signs

Vital signs (heart rate, blood pressure and temperature) will be obtained in the same position, either sitting or supine, as appropriate prior to any blood collection. All vital signs data

will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summary of notable vital sign values will be provided by treatment.

12-lead ECG data will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summaries of notable ECG value will be provided by treatment.

5 **Clinical Laboratory Evaluations**

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

10 CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v5.0, results will be categorized as low/normal/high (or other project-specific ranges, if more suitable) based on laboratory normal ranges.

15 The following summaries will be generated separately for hematology, and biochemistry tests:

- shift tables using CTCAE grades to compare baseline to the worst post-infusion value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)

20

All laboratory data will be listed with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

Tolerability

25 Tolerability of study drug will be assessed by summarizing the number of and reasons for dose delays and dose reductions. Dose intensity will also be tabulated by treatment group. Refer to Section 12.20.3.

12.20.4.1.3. Handling missing values / censoring / discontinuations

Subject safety data will be reported up to the cut-off date, end of post-treatment (if discontinued), death, lost to follow up, or withdrawal of consent, whichever happened first.

30 Missing values will not be imputed and will be reported as such.

12.20.4.1.4. Sensitivity Analyses

No formal sensitivity analysis is planned.

12.20.5. Analysis of secondary endpoints

The secondary efficacy endpoints used to assess the preliminary anti-tumor activity of BSBM3 or BSBM3 in combination with AL-102 are BOR, PFS, and DOR as per International Multiple Myeloma Working Group (IMWG) criteria (Section 12.24). All relative listings, tables and figures will be presented by treatment group, unless otherwise specified.

12.20.5.1. Efficacy endpoint(s)

Investigator assessment will be used in the main analysis of secondary endpoints that involve disease response. (including BOR, PFS and DOR). The main analysis of the secondary endpoints will be performed using the FAS.

10 Best overall response (BOR)

BOR is defined as the best response recorded from the start of the treatment until disease progression/recurrence as per local review and according to IMWG Criteria. BOR rate will be summarized Number of subjects achieving each category of response and percentages will be summarized by treatment group using FAS.

15 Overall response rate (ORR)

ORR is defined as the proportion of subjects with a BOR of sCR, CR, VGPR or PR, as per IMWG Criteria, local review. ORR for subjects in FAS will be summarized along with the 2-sided 90% exact Clopper-Pearson confidence intervals.

Complete Response Rate (CRR)

20 CRR is defined as the proportion of subjects with a BOR of sCR or CR, as per IMWG Criteria, local review. The CRR will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals.

Progression Free Survival (PFS)

25 PFS is defined as the time from the date of start of treatment to the date of the first documented progression as assessed using IMWG Criteria or death due to any cause. If a patient has not had an event, PFS is censored at the date of the last adequate assessment.

In case a patient does not have progression or death prior to data cutoff, PFS will be censored at the date of the last adequate assessment on or prior to the earliest censoring event. The censoring reason could be:

- 30**
- Ongoing without event
 - Lost to follow-up
 - Withdrew consent
 - New anticancer therapy for MM

- Event documented after at least two missing tumor assessments
- Adequate assessments no longer available

PFS will be summarized at the RDE and for all other treatment groups with at least 10 pts treated, using the Kaplan-Meier method. The median PFS as well as proportion of subjects without event at 3, 6, 9, and 12 months will be presented along with 95% confidence interval.

Duration of Response (DOR)

DOR applies only to subjects with a BOR of sCR, CR, VGPR or PR as assessed by IMWG. It is defined as the time from the date of first documented disease response (sCR, CR, VGPR or PR) to the date of first documented progression as assessed by IMWG or death due to MM. If a patient has not had an event, duration of overall response is censored at the date of the last adequate assessment.

In case a patient does not have progression or death due to MM prior to data cutoff, DOR follow the same censoring rules as for PFS.

DOR will also be summarized on the subset of subjects whose BOR is CR or better.

12.20.5.2. Pharmacokinetics

All subjects who have evaluable PK data will be included in the PK data analysis. PK parameters will be determined using non-compartmental method(s). PK parameters such as those listed in Table 18 will be estimated and reported, when applicable. Exploratory PK and PK/PD analysis may be conducted based on preliminary data prior to database lock, and nominal time instead of actual elapsed time may be used.

BSBM3, AL-102, and AL-102 metabolite plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

Pharmacokinetic parameters will be listed by treatment and subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented.

Descriptive graphical plots of individual concentration versus time profiles and mean concentration versus time profiles will be generated.

Table 18 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (λ_z) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL	The total body clearance of drug from the plasma (volume x time-1)
Vz	The volume of distribution during terminal phase (associated with λ_z) (volume)
AR	Accumulation Ratio = Cmax (multiple Dose)/Cmax (single dose)

12.20.5.3. Immunogenicity

To characterize the immunogenicity of BSBM3, the presence/absence of anti-BSBM3 antibody will be summarized by treatment groups. Analysis of exploratory endpoints

Analysis of exploratory endpoints will be detailed in the Statistical Analysis Plan (SAP).

5 12.20.5.4. Advanced data analysis and exploratory analysis

If feasible, exploratory PK analysis may be performed using non-linear mixed effects modeling to characterize the population PK and to estimate inter-individual variability in the study population. In addition, the emerging PK data may be compared to historical data from relevant studies or clinical reports to assess DDI potential.

10 Any analyses performed will be specified either in the Statistical Analysis Plan (SAP) prior to clinical database lock in an amendment to the SAP or in a stand-alone analysis plan document. All analyses will be reported either in the CSR or a stand-alone report.

12.20.6. Analysis of exploratory endpoints

15 All exploratory analyses intended to be discussed in the Clinical Study Report (CSR) will be defined in the Statistical Analysis Plan (SAP).

12.20.7. Interim analyses

20 No formal interim analyses are planned. However, the dose-escalation design allows that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose escalation, the next dose of study treatment will be selected based on review by Novartis study personnel and Investigators of available safety and tolerability information (including the DLT risk assessment from the B(H)LRM using EWOC) along with PK, PD and efficacy data. Details of this procedure and the process for communication with Investigators are provided in Section 12.11.

12.21. Sample size calculation**12.21.1. Primary endpoint(s)****Dose-escalation part**

Initially, cohorts of 1 to 6 evaluable subjects will be enrolled in the dose-escalation part.

5 Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 subjects may be enrolled at any dose level at or below a previously tested dose level, and satisfying EWOC, for further elaboration of safety and pharmacokinetic parameters as required. At least 21 subjects should be treated in the dose escalation part of single agent Arm A, and at least 18 subjects in the combination Arm B, for the model to have good operating

10 characteristics relating to the identification of the MTD amongst those doses tested (details in Section 12.25).

The MTD declaration will occur when the following conditions are met:

1. at least 6 treated subjects at the dose to be determined as the MTD
2. this dose satisfies one of the following conditions:
 - 15 a. the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
 - b. minimum of 21 treated subjects in single agent arm and a minimum of 18 subject in the combination arm on the trial.

Dose expansion part

20 For the dose expansion part, single agent BSBM3 and BSBM3 in combination with AL-102 will enroll approximately 20 subjects. The probability to detect a special interest of adverse event (AE) with a true incidence rate of 10% is 65.1% with 10 subjects, 79.4% with 15 subjects or 87.8% with 20 subjects respectively (Table 19).

Table 19 Probability to detect at least one special adverse event of interest

AE rate	Number of subjects			
	10	15	20	30
2.5%	0.224	0.316	0.397	0.532
5%	0.401	0.537	0.642	0.785
10%	0.651	0.794	0.878	0.958
15%	0.803	0.913	0.961	0.992

25

Table 20 shows the 95% credible intervals for a sample size of N = 10, 15, 20, and 30 for different number of responses using a minimally informative beta distribution as prior distribution with parameters b=1 and a=0.25 and prior mean 0.20 Note that the final interval will depend on the final sample size and the number of responses observed in each group.

Table 20 95% credible intervals for BSBM3 monotherapy (N = 10, 15, 20, and 30)

Observed responses	Observed response rate	Posterior mean	95% credible interval
N = 10			
1	0.1	0.111	(0.006,0.339)
2	0.2	0.2	(0.033,0.466)
3	0.3	0.289	(0.077,0.571)
4	0.4	0.378	(0.133,0.663)
5	0.5	0.467	(0.199,0.745)
6	0.6	0.556	(0.274,0.818)
N=15			
2	0.13	0.138	(0.022,0.337)
3	0.20	0.2	(0.05,0.419)
4	0.27	0.262	(0.086,0.492)
5	0.33	0.323	(0.127,0.561)
6	0.40	0.385	(0.172,0.624)
7	0.47	0.446	(0.221,0.684)
8	0.53	0.508	(0.274,0.739)
N=20			
3	0.15	0.153	(0.037,0.329)
4	0.2	0.2	(0.063,0.39)
5	0.25	0.247	(0.093,0.446)
6	0.3	0.294	(0.126,0.499)
7	0.35	0.341	(0.161,0.55)
8	0.40	0.388	(0.198,0.598)
9	0.45	0.435	(0.237,0.645)
10	0.50	0.482	(0.279,0.689)
N = 30			
4	0.13	0.136	(0.042,0.274)
5	0.17	0.168	(0.061,0.315)
6	0.20	0.2	(0.082,0.354)
7	0.23	0.232	(0.104,0.392)
8	0.27	0.264	(0.128,0.429)
9	0.30	0.296	(0.152,0.464)
10	0.33	0.328	(0.178,0.499)
11	0.37	0.36	(0.204,0.533)
12	0.40	0.392	(0.231,0.566)

12.22. Ethical considerations and administrative procedures

12.22.1. Regulatory and ethical compliance

- 5 This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

12.22.2. Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

12.22.3. Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT, etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

12.22.4. Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

12.23. Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects

should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data,
5 information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be
10 considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

12.23.1. Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the
15 IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator
20 is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

12.24. Guidelines for efficacy evaluation in Multiple Myeloma

25 12.24.1. Introduction and scope

The purpose of this document is to provide working definitions and rules to evaluate efficacy in multiple myeloma (MM).

This document is based on standardized response criteria as defined by the International Myeloma Working Group (IMWG) Uniform Response Criteria (Durie *et al.*, 2006, Leukemia 20:1467-1473), and also incorporated IMWG consensus criteria for response and
30 minimal residual disease assessments in multiple myeloma (Kumar *et al.*, 2016, Lancet Oncol 17:e328-46). These response criteria will be referred to as IMWG criteria. Other references were used to add recommendations.

More detailed instructions and rules for determination of best response are given as well as specifications for the analysis of time-to-event variables. Moreover, this document describes data handling and derivation rules.

12.24.2. Efficacy Assessments

5 12.24.2.1. General

12.24.2.1.1. Measurable Disease

For the IMWG criteria, measurable disease based on protein assessment is defined as at least one of the following conditions present at baseline (Kumar *et al.*, 2016, Lancet Oncol 17:e328-46)

- 10 • Serum M-protein by PEP ≥ 1.0 g/dL
- 24h-urine M-protein by PEP ≥ 200 mg/24h
- Involved serum FLC level ≥ 10 mg/dL (≥ 100 mg/L) provided the FLC ratio is abnormal (Section 12.24.2.2.2)

15 In case of none of the criteria applies, the patient is considered to have non-measurable disease.

12.24.2.1.2. Eligibility

20 In general, only patients with measurable disease (e.g., according to (Section 12.24.2.1.1) should be included in a trial. In case a patient with non-measurable disease was enrolled, disease assessment should be continued with bone marrow aspiration / biopsy and a protocol deviation should be documented.

12.24.2.1.3. Definition of lines of therapy

25 A line of therapy consists of one or more planned cycles of either single agent or combined therapy, as well as a sequence of treatments administered in a planned manner (e.g. autologous stem cell transplant, followed by maintenance, is considered only one line of therapy).

A line of therapy ends at the planned treatment completion, disease progression, relapse, discontinuation of treatment due to toxicity, start of an unplanned anti-MM therapy or death (Rajkumar *et al.*, 2011, Blood 117(18):4691-4695).

12.24.2.1.4. Baseline assessments

30 Assessments to be performed at baseline include:

- M-protein in serum and urine by PEP (Section 12.24.2.2.1)
- M-protein in serum and urine by immunofixation (IF) (Section 12.24.2.2.1)
- Serum FLC ratio (Section 12.24.2.2.2)

- Plasma cell count in bone marrow (Section 12.24.2.2.3)
 - Clinical assessment for soft tissue plasmacytomas. In case of known or detectable soft tissue plasmacytoma at baseline, further confirmation and measurements are required at baseline by imaging techniques (CT/MRI) (Section 12.24.2.2.5)
 - Full body skeletal survey by X-ray; full body CT scan and full body MRI are also accepted if X-rays cannot be performed (Section 12.24.2.2.6)
 - Routine biochemistry including ionized calcium or total serum calcium and albumin (Section 12.24.2.2.7)
- 10 For baseline assessments, no confirmation measurement is required.

12.24.2.1.5. Post-baseline assessments

Assessments to be performed at post-baseline visits include:

- M-protein in serum and urine by PEP (Section 12.24.2.2.1)
- M-protein in serum and urine by IF (Section 12.24.2.2.1)
- Serum FLC assessment if patient has non-measurable disease in serum and urine M-protein at baseline (Section 12.24.2.2.2)
- Soft tissue plasmacytomas (STP) (Section 12.24.2.2.5)
- Lytic bone lesions assessment, if clinically indicated (Section 12.24.2.2.6)
- Serum calcium and albumin or ionized calcium (Section 12.24.2.2.7)
- Plasma cell count in bone marrow by aspirate or biopsy in patients who met all criteria for CR by serum and urine M protein with no indication of disease progression by STP, lytic bone lesions and hypercalcemia or in case of non-measurable disease by M protein in serum and urine by PEP and by FLC (Section 12.24.2.2.3)
- Residual disease by flow cytometry/ immunohistochemistry in bone marrow plasma cells in case of CR criteria are met (Section 12.24.2.2.4)

12.24.2.1.6. Time frame of response assessments

For the baseline assessment, the last available measurement for a variable prior to first intake of study treatment has to be used. Baseline assessments should be done prior to the first intake of study treatment and within a time window defined by the protocol.

All measurements required for a response assessment post-baseline should be performed within a predefined time window. The time window(s) should be specified in the study protocol.

In case there is more than one measurement of any variable in the predefined time window, the latest non-missing measurement of this variable will be used. Exception: In case of one measurement qualifying for PD, this will be used for the response assessment irrespective of subsequent measurements of the same variable.

12.24.2.1.7. Response assessment date

The response assessment date is defined as the last of all dates of measurements which are required to qualify for a response category (excluding PD). In case of PD, the first of all measurement dates associated with a disease assessment will be used as assessment date. The response assessment date will be used for the derivation of the time-to-event endpoints.

12.24.2.1.8. Nadir

The nadir is defined as the lowest value of a variable including baseline measurements excluding the measurement of the respective visit. This rule implies that the time point of determination of the lowest value of a patient may be different for each variable.

12.24.2.1.9. Staging of Multiple Myeloma

Staging of MM should be done according the International Staging System (ISS, Greipp *et al.*, 2005, J Clin Onc 23(15):3412-3420; FIG. 7).

12.24.2.2. Test required for response assessment

12.24.2.2.1. Assessment of M-protein in serum and urine

The assessment of the M-protein levels in serum and urine is the basis for the response assessments for multiple myeloma. The following two methods are used to assess M-protein in serum as well as in urine.

1. Protein electrophoresis (PEP): Provides quantitative measurements. Techniques other than electrophoresis are not acceptable unless specifically mentioned in this document.
2. Immunofixation (IF): Provides qualitative measurements (present/absent). This is a more sensitive method than PEP and is used to confirm the absence of M-protein by PEP.

For M protein in urine by PEP, a 24h urine collection is required.

The PEP has to be performed to assess serum and urine M-protein levels at baseline and post baseline. Even if disease is non-measurable, both serum and urine should routinely be tested for PEP post baseline.

In case no M-protein is found by electrophoresis, this should be confirmed by serum/urine immunofixation.

In case serum/urine M-protein was not assessed by PEP and the corresponding serum/urine immunofixation results indicate absence of M-protein, it can be concluded that there is no M-protein identifiable by PEP in serum/urine.

12.24.2.2.2. Assessment of free light chain proteins (FLC)

The free light chain (FLC) assessment was introduced by the IMWG using serum FLC assay (FREELITE, The Binding Site Ltd., Birmingham, UK) which is performed by immunonephelometry (Dispenzieri *et al.*, 2009, Leukemia 23: 215-224).

The serum FLC assay measures

1. Free kappa light chain (also known as kappa serum level) (reference interval, 0.33-1.94 mg/dL) and
2. Free lambda light chain (also known as lambda serum level) (reference interval, 0.57-2.63 mg/dL)

The FLC ratio is defined as the kappa serum level divided by the lambda serum level.

Involved light chain is determined based on the following criteria (Snozek *et al.*, 2008, Leukemia 22:1933-1937):

1. Lambda is the involved light chain if FLC ratio < 0.26
2. Kappa is the involved light chain if FLC ratio of > 1.65

The FLC ratio is considered to be

- Normal if FLC ratio is within [0.26-1.65]
- Abnormal if FLC ratio is <0.26 or >1.65

The FLC serves as indicator of disease status when serum M-protein and urine M-protein assessed by PEP is/are non-measurable and to identify sCR in case CR criteria are met (Table 21).

12.24.2.2.3. Assessment of bone marrow for percentage of plasma cells

Bone marrow should be assessed for percentage of plasma cells. Either bone marrow aspirate or biopsy can be used for this assessment. The same method (aspirate versus biopsy) should be used throughout the trial, if possible. In case both aspirate and biopsy were done, the response criteria need to be satisfied by both assessments. In case both aspirate and biopsy are performed, the highest of both percent values should be used for the assessment.

Bone marrow samples are usually drawn from either sternum or iliac crest. Percentage of plasma cells will be determined by using cytological/histological examination.

In case of inadequate/uninterpretable bone marrow sample, the sampling must be repeated in a timely manner but no later than within the protocol-defined time window (Section 12.24.2.1.5).

12.24.2.2.4. Assessment of MRD

5 The two most widely used methods for assessing residual neoplastic plasma cells (PC) in the bone marrow are flow cytometry and immunohistochemistry.

Flow cytometry

10 IMWG criteria require assessment of clonal plasma cells for assessment by standard flow cytometry (using 2 to 4 colors). Bone marrow aspirates will be analyzed by multiparametric flow cytometry (MFC) and/or molecular analysis of Ig gene rearrangements (deep sequencing) to assess for Minimal Residual disease (MRD).

If there are no bone marrow elements and no plasma cells in the sample, this will be considered not to be suitable for analysis and will need to be repeated.

Immunohistochemistry

15 Immunohistochemistry is used to differentiate normal from clonal PCs in the bone marrow for assessment of sCR. Presence/absence of clonal cells is based upon the kappa/lambda (k/l) ratio. An abnormal k/l ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l ratio of $> 4:1$ or $< 1:2$ (Kumar *et al.*, 2016, Lancet Oncol 17:e328-46).

20 12.24.2.2.5. Assessment of soft tissue plasmacytomas

General definitions

- The size of the soft tissue plasmacytomas is defined as the sum of the products of the maximal perpendicular diameters (SPD) of each soft tissue plasmacytoma.
- A definite increase in the size is defined as a $\geq 50\%$ increase (and at least 10 mm²) of this sum from the nadir.

Assessment of soft tissue plasmacytomas

1. For soft tissue plasmacytoma(s) present at baseline per clinical assessment:
 - imaging by CT or MRI must be performed at baseline to confirm and to determine size and location of the soft tissue plasmacytoma.
- 30 Size and location of soft tissue plasmacytoma(s) will be monitored by imaging at regular intervals according to the requirements of the individual study protocol.

2. In case of clinical suspicion of (re-)appearance of a soft tissue plasmacytoma post-baseline, imaging by CT or MRI must be performed as soon as possible to confirm and to determine size and location of the soft tissue plasmacytoma.

3. Size and location of identified soft tissue plasmacytoma(s) should be captured on the
5 CRF.

a. The size should be captured in terms of longest perpendicular diameters

b. If any of the perpendicular diameters cannot be reliably measured because of its small size, the minimum limit of detection as the diameter size (e.g. 7.5 mm for CT) should be entered.

10 c. A value of 0 mm x 0 mm should be entered in case of disappearance of a soft tissue plasmacytoma

The same imaging technique must be used through the course of the trial to monitor an existing soft tissue plasmacytoma. CT and MRI should be performed with slice thickness ≤ 7.5 mm.

15 If soft tissue plasmacytomas become confluent over time, then these should be measured as one soft tissue plasmacytoma. The overall diameters should be recorded for one of the soft tissue plasmacytomas, and 0 mm x 0 mm should be recorded for the rest of the soft tissue plasmacytomas.

20 If a soft tissue plasmacytoma splits during the study, each part of the soft tissue plasmacytoma should be measured separately for all subsequent assessments and all parts of the soft tissue plasmacytoma should contribute to the SPD.

12.24.2.2.6. Assessment of lytic bone lesions

25 Full body skeletal survey using conventional X-rays (preferred method) or CT or MRI should be performed prior to study treatment start. Based on the currently available evidence, PET is not recommended to be used for the assessment of lytic bone lesions (Dimopoulos *et al.*, 2009, International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple Myeloma. Leukemia online publication: 1-12; Rajkumar *et al.*, 2014, Lancet Onc 15:e538-548).

30 Interpretation of full body skeletal survey (in terms of presence or absence of lytic bone lesion, number (categories) and location of lesions) will be captured on the CRF.

Targeted post baseline assessments using bone X-ray/CT/MRI on location(s) should be performed if there is any medical indication (e.g. bone pain) as determined by the investigator. The following information will be captured on the CRF: absence/ presence, lesion location, unchanged, new lesion(s) or increase in size of existing lesion(s).

The same imaging technique at baseline and post-baseline should be used for comparison of lytic bone lesion assessments. In case of new symptomatic areas, with no finding by X-ray, targeted MRI or CT assessment should be performed.

12.24.2.2.7. Assessment of hypercalcemia

5 Hypercalcemia is assessed based on corrected or ionized serum calcium.

In case total serum calcium is measured, the value needs to be corrected for serum albumin according to the following formula (Ladenson *et al.*, 1978, J Clin Endocrinol Metab 48:393-397):

10
$$\text{Corrected serum calcium [mg/dL]} = \text{measured total serum calcium [mg/dL]} + (3.5 - \text{serum albumin [g/dL]}) \times 0.8.$$

It is not acceptable to use uncorrected total calcium to assess hypercalcemia.

Corrected serum calcium values > 11.5 mg/dL indicate hypercalcemia. In case ionized serum calcium is measured, no correction for serum albumin is required and values > 6.0 mg/dL indicate hypercalcemia.

15 In case corrected serum calcium and ionized calcium are measured at the same visit, the ionized calcium value will be used for response assessment. It is recommended to use the same method throughout the trial.

12.24.2.3. Response assessment per IMWG criteria

20 Response assessment according to IMWG criteria is described in Table 21 and Table 22. For assessing response, criteria for PD should be assessed first. When PD can be ruled out, criteria for positive response should be checked.

For patients with non-measurable disease at baseline or missing baseline assessments of M protein in urine and serum and FLC, only PD criteria will be checked. In case PD is not met, "unknown" should be assigned.

25 Confirmation of response requires two consecutive readings of the applicable disease parameter. The criteria are defined in Section 12.24.2.3.1 and Section 12.24.2.3.2. For MRD, there is no need for two consecutive assessments.

For patients with measurable disease at baseline by one component only (serum M-protein or urine M-protein), the measurable component will be used to derive MR or PR.

30 However, VGPR and CR categories require serum and urine measurements regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Irrespective of the measurability (M protein measurable by PEP in serum, urine, or both), M-protein should be investigated regularly in both serum and urine and needs to be considered for response assessment.

Assessments to determine PD are dependent on change from nadir.

Table 21 Response classification in MM according to IMWG criteria

Response category	Definition*
Stringent complete response (sCR)	CR criteria as defined below AND normal FLC ratio AND Absence of clonal PCs in bone marrow analyzed by immunohistochemistry#.
Complete response (CR)	Negative immunofixation of serum and urine AND In case of presence of soft tissue plasmacytoma(s) at baseline, disappearance of any soft tissue plasmacytoma(s), AND < 5% plasma cells in bone marrow. In case the only measurable disease at baseline is the serum FLC assessment, a normal FLC ratio of 0.26 to 1.65 is required additionally to qualify for CR.
Very good partial response (VGPR)	Serum and/or urine M-protein detectable by immunofixation but not on PEP OR (≥ 90% reduction from baseline in serum) AND (24h-urine M-protein < 100 mg/24h) For patients achieving very good partial response by other criteria, a soft tissue plasmacytoma must decrease by more than 90% in the sum of the maximal perpendicular diameter (SPD) compared with baseline In case the only measurable disease in a patient at baseline is the serum FLC level (i.e. no measurable disease in serum and urine PEP), a decrease of > 90% in the difference between involved and uninvolved FLC levels from baseline is required.
Partial response (PR)	(≥ 50% reduction from baseline in serum M-protein) AND (≥ 90% reduction from baseline in 24h-urine M-protein OR 24h-urine M-protein < 200 mg/24h) If the serum and urine M-protein are not measurable at baseline a ≥ 50% reduction from baseline in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum FLC assay is also not measurable, ≥ 50% reduction from baseline in plasma cells in bone marrow is required instead of M-protein measurement, provided baseline percentage in plasma cells in bone marrow was ≥ 30%. AND In case of presence of soft tissue plasmacytoma(s) at baseline, a reduction in the SPD (Section 12.24.2.2.5) by ≥ 50% is required.
Minimal response (MR)	(Reduction from baseline in serum M-protein by ≥25 - 49%) and (reduction from baseline in 24h urine M-protein by ≥50 - 89%) AND In case of soft tissue plasmacytomas at baseline, a reduction in the size of ≥50% is required
Stable disease (SD)	Not meeting the criteria for sCR, CR, VGPR, PR, PD
Progressive disease (PD)	Increase of at least 25% from the nadir in at least one of the following criteria: Serum M-protein (absolute increase must be ≥ 0.5 g/dL) or serum M-protein increase ≥1 g/dL, if the lowest M component was ≥ 5 g/dL 24h-urine M-protein (absolute increase must be ≥ 200 mg/24h) Only in patients without measurable serum and urine M-protein levels: difference in involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) Only in patients without measurable serum and urine M-protein levels and without measurable involved FLC levels: bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be ≥ 10%)

Response category	Definition*
	Appearance of a new lesion(s), $\geq 50\%$ increase from nadir in SPD >1 lesion, or $\geq 50\%$ increase in the longest diameter of a previous lesion > 1 cm in short axis; $\geq 50\%$ increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease. Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or ionized calcium > 6 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

* If not defined otherwise, all of the criteria apply.

Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of $> 4:1$ or $< 1:2$.

- 5 In case response assessment is incomplete, e.g. one or more mandatory assessments are missing, at a time point then the category “unknown” will be assigned to the response assessment of that time point unless a criterion for PD is met.

In addition to the criteria above, Minimal Residual Disease (MRD) will be assessed (Kumar 2016) using bone marrow aspirates. MRD will be investigated at the time-points
10 mentioned in the protocol.

Table 22 Additional response categories in MM

Response category	Definition*
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD-negative at 5 years).
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher

Sustained MRD-negativity will be assessed only for patients who continue the study for at least 12 months after the first MRD-negativity assessment using the same method.

12.24.2.3.1. Confirmation of Response

- 15 According to IMWG criteria, confirmation of response is required for all response categories other than MR and SD. For MRD, a confirmation assessment is not required. The intention of this confirmation is to rule out laboratory or other errors (Kumar *et al.*, 2016, Lancet Oncol 17:e328-46). For response confirmation, a consecutive assessment at any time is

required; no time window is specified by IMWG. Therefore, confirmation assessment can be performed on the same day of the initial assessment. This confirmation should be obtained in all instances by M-protein assessments (tests may include part or all of tests PEP/FLC depending on measurability and response level).

- 5 Response assessments should be captured in the CRF per time point without considering confirmation.

For confirmation of response, the following rules apply which will be implemented for statistical analyses:

- 10 • It is not required to repeat assessments on bone marrow. However, at least one bone marrow assessment is required to qualify for CR or better.
- In case imaging studies were done, it is necessary that they exclude evidence of PD with regard to new lytic bone lesions for sCR, CR, VGPR, PR, MR and SD. Imaging is indicated in case of clinical suspicion of new or worsened lytic bone lesions e.g. bone pain.
- 15 • In case the confirmation assessment revealed a better category compared to the previous assessment (e.g. VGPR after PR), the response category of the previous assessment will be considered as confirmed (PR).
- In case the confirmation assessment revealed a worse category compared to the previous assessment (e.g. VGPR after CR), the response category of the subsequent assessment will be considered as confirmed (VGPR).
- 20 • In case of repeated measurements of a variable at a given response assessment resulting in more values than required for an assessment and confirmation, the worst assessment has to be considered for response assessment by applying the rules given above.

25 12.24.2.3.2. Confirmation of PD

Declaration of PD requires confirmation in case the PD was determined based on M-protein measurement. There is no minimum time interval but confirmation of increase in M-protein or FLC should be done as soon as possible and PD assessment has to be entered in the CRF. PD has to be assessed and entered in the CRF per time point without considering confirmation. Confirmation of PD will be programmed in statistical analyses.

12.24.3. Derivation Rules

12.24.3.1. Best overall response and overall response

Best overall response is the best post baseline confirmed overall response observed in a given patient, among the confirmed response categories, excluding “unknown” and “not assessed”. Best overall response is determined based on overall responses observed at all

post-baseline response assessments, recorded from the start of the study treatment until PD, death, start of new therapy, withdrawal of consent or end of study, whatever comes first.

If the first complete post-baseline response assessment indicates PR or better (VGPR, CR or sCR) and no confirmation response assessment available then SD will be considered as
5 best overall response.

Best overall response will be assigned according to the following ascending order (Table 23).

Table 23 Best overall response

Rank	Best overall response category
1	Stringent Complete Response (sCR)
2	Complete Response (CR)
3	Very Good Partial Response (VGPR)
4	Partial Response (PR)
5	Minimal Response (MR)
6	Stable Disease (SD)
7	Unknown
8	Progressive disease (PD)

10 In case no post-baseline assessment is available or assessments with only unknown response status are available, the category “unknown” will be assigned as best overall response.

Based on the patients’ best overall response during the study, the following rate is calculated:

15 Overall response rate (ORR) is the proportion of patients with best overall response of PR or better. For the calculation of the ORR, the denominator should include all patients in the targeted patient population. Additional analysis sets can be defined in the study protocol.

MR can be an indicator of drug activity in certain patient populations, and in particular for patients with relapsed as well as relapsed and refractory MM. In case MR is used, the rate
20 of patients with MR should be reported separately from the ORR (Rajkumar 2011).

12.24.3.2. Calculation of time-to-event variables

General rule for the calculation of the time to event interval is:

Time to event = end date - start date + 1 (in days)

When no post-baseline response assessment is available, the date of start of study
25 treatment will be used as end date (duration = 1 day), i.e. time to event variables will never be negative.

12.24.3.2.1. Adequate response assessment

Often censoring time is determined based on date of adequate response assessment. Any response assessment is considered to be adequate if the assessment was performed and the outcome of the assessment was other than “unknown” or PD.

5 12.24.3.2.2. Overall survival

Overall survival (OS) is defined as the time from date of start of study treatment to the date of death due to any cause.

If a patient is alive or his/her survival status is unknown, OS will be censored at the date of last contact.

10 12.24.3.2.3. Progression-free survival

Progression-free survival (PFS) is defined as time from date of start of study treatment to date of (1) death due to any cause or (2) PD.

If a patient has not had an event, PFS is censored at the last adequate response assessment date.

15 12.24.3.2.4. Time to progression

Time to progression (TTP) is defined as the time from the date of start of study treatment to the date of (1) death due to multiple myeloma or (2) PD.

If a patient has not had an event, TTP is censored at the last adequate response assessment date.

20 12.24.3.2.5. Duration of response

Duration of response (DOR) is defined as the duration from the first documented onset of PR or better response to the date of PD or death due to multiple myeloma.

In case a patient does not have PD or death due to multiple myeloma, DOR will be censored at the date of the last adequate assessment.

25 12.24.3.2.6. Time to response

Time to response (TTR) is defined as the time between date of start of study treatment to the date of first onset of PR or better response.

Patients without experiencing any PR or better response will be censored according to the following events:

- 30**
- Patients experiencing a PD will be censored at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients (i.e. either progressed or died due to any cause)
 - Patients not experiencing PD will be censored at their last adequate response assessment date.

Table 24 Censoring rules for time to response

Situation		Start-date	End-date	Outcome
A	PR or better	Date of start of treatment	Date of first onset of confirmed PR or better (before cut-off date and before start of new anti-neoplastic therapy)	Event
B	PD/Death	Date of start of treatment	At maximum follow-up (i.e. FPFV to LPLV used for the analysis)	Censor
C	No PR or better and no PD/death	Date of start of treatment	Date of last adequate response assessment before cut-off date and before start of new anti-neoplastic therapy	Censor

12.24.3.2.7. Time to next treatment

Time to next treatment (TNT) is defined as the time from the date of start of study treatment to the date of next treatment for multiple myeloma or death due to any cause. The need to start the next treatment should be defined clearly in the protocol. This should be the case in either clinical relapse or significant paraprotein relapse. Start of new anti-neoplastic treatment without meeting the relapse criteria is also considered as event.

In case a patient does not experience a relapse event and does not start new anti-neoplastic therapy, time to next treatment will be censored at the last adequate response assessment.

Clinical relapse is defined as one or more of the following indicators that are related to the underlying MM:

- Direct indicators of increasing disease and/or end organ dysfunction related to the underlying clonal plasma-cell proliferative disorder.
- Definite development of new lytic bone lesions or definite increase from baseline in size of lytic bone lesion(s)
- Definite development of new soft tissue plasmacytoma(s) or definite increase from nadir in existing soft tissue plasmacytomas
- Hypercalcemia(> 11 mg/dL)
- Decrease in hemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions
- Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma
- Hyperviscosity related to serum paraprotein

12.24.3.3. Event and censoring date, sensitivity analysis

This section outlines the possible event and censoring dates for PD (Table 25), as well as addressing the issues of missing response assessments during the study. It is important that

the protocol and analysis plan specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed. Using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 25 Options for event dates used in PFS and TTP

Situation	Options for end-date (1) = default unless specified differently in the protocol or analysis plan	Outcome
A No baseline assessment	(1) Date of <i>start of treatment</i>	Censor
B PD or death ¹ at scheduled assessment date or before next scheduled assessment	(1) Date of PD (or death) (2) Date of next scheduled assessment	Event Event
C1 PD or death ¹ after exactly one missing assessment	(1) Date of PD (or death) (2) Date of next scheduled assessment	Event Event
C2 PD or death ¹ after two or more missing assessments	(1) Date of last adequate assessment (2) Date of next scheduled assessment (3) Date of PD (or death)	Censor Event Event
D No PD and no death	(1) Date of last adequate assessment	Censor
E Treatment discontinuation due to 'Disease PD' without documented PD, i.e. clinical PD based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical PD was determined)	Ignored Event
F New anticancer therapy given	(1) Date of last adequate assessment prior to start of new anti-cancer therapy (2) Date of new anti-cancer therapy (3) Date of new anti-cancer therapy (4) N/A	Censor Censor Event Not considered as event
G Death due to reason other than multiple myeloma	(1) Date of last adequate assessment	Censor (only TTP)

¹ PFS: death due to any reason; TTP: death due to MM; PD – disease progression

In case a patient does not have an adequate assessment and the date of start of study treatment is used as end date.

10 Situations C (C1 and C2): PD or death after one or more missing assessments:

The primary analysis in this study is using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual PD or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

15 In the case of two or more missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this

sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'PD' without documented PD: option (1) is used for situation E as patients without documented PD should be followed for PD after discontinuation of treatment. However, option (2) may be used as sensitivity analysis.

Situation F: New cancer therapy given: the handling of this situation is specified in detail in the protocol. Option (1), i.e. censoring at last adequate assessment is considered in the primary analysis of PFS.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for response assessments, e.g.:

- By assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 25 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

Date of previous scheduled assessment (from baseline) is the date when a response assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate assessment.

- By considering any appearance or recurrence of clinical indicators not part of the criteria list but mentioned in the IMWG criteria, in particular "bone pain".

The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the Study Protocol or Statistical Analysis Plan (SAP).

12.25. Statistical considerations

This appendix provides details of the statistical model, the derivation of prior distributions from pre-clinical data, the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model.

12.25.1. Statistical model

Let $\pi(d)$ be the risk of DLT for BSBM3 given at dose d , the dose-DLT model is logistic:

$$\text{"logit"}(\pi(d)) = \text{"log"}(\alpha) + \beta \text{"log"}(d/d^*)$$

where $d^*=200$ mcg/kg is used as a reference to scale the doses of BSBM3. Hence, α (>0) is the odds of a DLT at d^* mg; and β (>0) is the increase in the log-odds of a DLT by a unit increase in log-dose.

12.25.2. Prior specifications

The Bayesian approach requires the specification of prior distributions for the model parameters "log" (α) and "log" (β). Based on pre-clinical toxicology data, weakly informative priors were derived for these parameters.

5 12.25.2.1. Prior distribution of logistic parameters

A weakly informative mixture prior was derived.

Component 1

Weakly informative bivariate normal prior for the model parameters were elicited based on information (medians of probability of toxicity) gathered from pre-clinical data displayed in
 10 Table 26 for cynomolgus monkeys (Example 2). The prior was then obtained by finding the optimal quantile matching bivariate normal distribution via stochastic Metropolis optimization.

Table 26 Summary of pre-clinical study in monkeys and the prior (guess) median probability of toxicity

Study/Species	Human equivalent dose (mcg/kg)	Median prior Pr(DLT)
Monkey	30	0.005
	1000	0.33

15 Based on data from pre-clinical study, a dose of 30 mcg/kg is considered to be safe with low DLT rate. Therefore, a rate of 0.5% is assumed at this dose level. In addition, a prior toxicity rate of 33% is assumed for the 1000 mcg/kg dose because this is the human equivalent dose based on an integrated assessment of the proposed mechanism of action, target biology, in vitro pharmacology studies and in vivo safety in the cynomolgus monkeys GLP toxicology
 20 study.

Component 2

To make the prior more robust, an additional mixture component corresponding to high toxicity was introduced. For this component the median probability of DLT at dose 200 mcg/kg was assumed to be 20%.

25 For all mixture components, the median for the prior distribution of "log" (β) was set to 0, to correspond to a doubling of dose leading to a doubling of the odds of DLT. Standard deviations for "log" (α) and "log" (β) were set to 2 and 1 respectively, with correlation $\rho=0$, corresponding to a weakly-informative prior.

30 The mixture components were weighted based upon a priori assessment of their relevance to the toxicity of BSBM3 in humans, where 80% weight is assigned to the pre-clinical data and 20% weight is assigned to the "high toxicity" component.

12.25.2.2. Summary of prior distributions

Table 27 summarizes the prior distributions for the model parameters. Table 28 summarizes the prior distribution of the DLT rates. The doses not meeting the overdose control criterion are bolded in the table, i.e., doses not eligible at the start of the study (under the prior).

5 As noted below, doses of 192 mcg/kg and higher cannot be used as starting dose.

Table 27 Prior distribution of model parameters

Model component	Weight	Means: ($\log(\alpha)$, $\log(\beta)$)	Standard deviations: ($\log(\alpha)$, $\log(\beta)$)	Correlation: ($\log(\alpha)$, $\log(\beta)$)
Monkey	0.8	(-2.588, -0.076)	(2.473, 0.630)	-0.611
High toxicity	0.2	(-1.386, 0)	(2, 1)	0

Table 28 Summary of prior distribution of DLT rates

Dose (mcg/kg)	Prior probabilities that Pr(DLT) is in interval:			Mean	SD	Quantile		
	[0-0.16]	[0.16-0.33]	[0.33-1.0]			2.5%	50%	97.5 %
3	0.903	0.042	0.056	0.055	0.15	0	0.001	0.61
6	0.883	0.05	0.067	0.066	0.163	0	0.003	0.67
12	0.858	0.06	0.083	0.08	0.178	0	0.006	0.725
24	0.824	0.073	0.104	0.098	0.195	0	0.011	0.776
48	0.777	0.09	0.132	0.123	0.215	0	0.021	0.824
96	0.711	0.113	0.176	0.158	0.237	0	0.042	0.868
192	0.613	0.141	0.246	0.213	0.264	0.001	0.086	0.908
384	0.488	0.161	0.351	0.292	0.299	0.003	0.169	0.959
600	0.401	0.169	0.43	0.352	0.315	0.005	0.25	0.98

10 12.25.3. Hypothetical on-study data scenarios

To illustrate the performance of the Bayesian model used to guide dose escalation, hypothetical dose escalations scenarios following the provisional dose levels specified in Table 29 are displayed. In each case, the maximum dose that can be used in the next cohort of patients is shown. This maximum tolerated dose is determined using the model based assessment of the risk of DLT in future patients and the dose escalation rules as described in Table 28. In practice a dose below the maximum might be chosen based on additional safety, PK or PD information (Section 12.11.2.1).

Table 29 Hypothetical dose escalation scenarios

Scenario	BSBM3 Dose (mcg/kg)	BSBM3 Ntox/Npat	BSBM3 Next dose (mcg/kg)	P(Target) Next dose	P(Overdose) Next dose	Median DLT rate Next dose
1	3	0/1	6	0.041	0.033	0.002
2	3	0/1	12	0.038	0.017	0.003
	6	0/2				
3	3	0/1	6	0.269	0.176	0.136
	6	1/3				
4	3	0/1	12	0.303	0.136	0.140
	6	1/3				
	6	0/2				
5	3	0/1	3	0.372	0.211	0.189
	6	1/3				
	6	1/2				
6	3	0/1	24	0.298	0.096	0.124
	6	1/3				
	6	0/2				
	12	0/3				
7	3	0/1	12	0.425	0.205	0.201
	6	1/3				
	6	0/2				
	12	1/3				
8	3	0/1	6	0.464	0.163	0.195
	6	1/3				
	6	0/2				
	12	2/5				
9	3	0/1	24	0.434	0.201	0.203
	6	1/3				
	6	0/2				
	12	1/6				
10	3	0/1	24	0.039	0.012	0.005
	6	0/2				
	12	0/2				
11	3	0/1	24	0.314	0.181	0.158
	6	0/2				
	12	1/3				
12	3	0/1	24	0.311	0.142	0.143
	6	0/2				
	12	1/4				
13	3	0/1	48	0.309	0.119	0.134
	6	0/2				
	12	1/4				
	24	0/3				
14	3	0/1	24	0.432	0.204	0.204
	6	0/2				
	12	1/4				
	24	1/3				
15	3	0/1	12	0.479	0.138	0.190
	6	0/2				
	12	1/4				

Scenario	BSBM3 Dose (mcg/kg)	BSBM3 Ntox/Npat	BSBM3 Next dose (mcg/kg)	P(Target) Next dose	P(Overdose) Next dose	Median DLT rate Next dose
16	24	2/5	48	0.441	0.232	0.217
	3	0/1				
	6	0/2				
	12	1/4				
17	24	1/6	96	0.325	0.118	0.141
	3	0/1				
	6	0/2				
	12	1/4				
18	24	0/3	48	0.454	0.174	0.197
	48	0/3				
	3	0/1				
	6	0/2				
19	12	1/4	96	0.452	0.207	0.214
	24	0/3				
	48	1/3				
	3	0/1				
20	6	0/2	192	0.335	0.128	0.148
	12	1/4				
	24	0/3				
	48	0/3				
21	96	0/3	96	0.430	0.128	0.176
	3	0/1				
	6	0/2				
	12	1/4				
22	24	0/3	192	0.460	0.207	0.213
	48	1/6				
	96	0/4				
	3	0/1				
23	6	0/2	192	0.440	0.231	0.214
	12	1/4				
	24	0/3				
	48	0/3				
24	96	1/6	96	0.475	0.072	0.172
	3	0/1				
	6	0/2				
	12	1/4				

Scenario	BSBM3 Dose (mcg/kg)	BSBM3 Ntox/Npat	BSBM3 Next dose (mcg/kg)	P(Target) Next dose	P(Overdose) Next dose	Median DLT rate Next dose
25	24	0/3	192	0.526	0.116	0.196
	48	1/6				
	96	0/4				
	192	1/3				
	3	0/1				
	6	0/2				
	12	¼				
	24	0/3				
	48	1/6				
	96	0/4				
26	192	1/6	384	0.442	0.234	0.218
	3	0/1				
	6	0/2				
	12	¼				
	24	0/3				
	48	1/6				
	96	0/4				
	192	0/3				
27	3	0/1	384	0.524	0.215	0.226
	6	0/2				
	12	¼				
	24	0/3				
	48	1/6				
	96	0/4				
	192	0/3				
28	384	¼	192	0.589	0.111	0.205
	3	0/1				
	6	0/2				
	12	¼				
	24	0/3				
	48	1/6				
	96	0/4				
	192	0/3				
	384	2/5				

*Intermediate dose level, where a higher provisional dose is not allowed by the BLRM model, a lower dose level is selected according to the protocol Section 12.11.1.2

5 12.25.4. Operating characteristics

A simulation study is used to illustrate the long run performance of the Bayesian dose escalation model. Several example scenarios were investigated (Table 30), and in each case 1000 trials were simulated, with results summarized in Table 31.

Scenarios

In order to show how the design performs, 4 hypothetical scenarios were investigated:

1. Scenario 1 represents a scenario which is in line with the prior, i.e. the true underlying toxicity is set to the median values of the prior.
- 5 2. Scenario 2 represents a scenario assuming high toxicity, i.e. the true underlying toxicity is higher than what would be predicted from the prior,
3. Scenario 3 represents a scenario assuming lower toxicity, i.e. the true underlying toxicity is lower for what would be predicted from the prior.
- 10 4. Scenario 4 represents a scenario assuming much higher toxicity, i.e. the true underlying toxicity is higher than 50% for all dose levels.

The true probabilities used in the simulation are presented in Table 30 for each scenario above.

Table 30 True probability of DLT for simulation scenarios

BSBM3 single dose (mcg/kg)	30	100	200	400	600
Scenario 1	0.013	0.043	0.089	0.173	0.245
Scenario 2	0.026	0.082	0.163	0.295	0.394
Scenario 3	0.01	0.033	0.068	0.136	0.196
Scenario 4	0.55	0.70	0.80	0.85	0.9

Simulation details

1000 trials were used to simulate each scenario. The starting dose was chosen as 30 mcg/kg single dose at Day 1. The provisional doses to jump to follows the protocol specifications and are 100, 200, 400, 600 mcg/kg single dose Q1W. The number of patients to enroll in each cohort and stopping rule used to declare MTD were defined as:

- 20 • Minimum cohort size: 3
- Maximum cohort size: 6
- Minimum number of patients to be treated in the trial: 21
- Minimum number of patients treated at a given dose in order to declare MTD: 6

Metrics

- 25 Operating characteristics were reviewed for the simulations to compare the relative performance under each true probability scenario. The metrics reviewed were:

1. Average proportion of patients receiving a target dose on study (I)

2. Average proportion of patients receiving a dose with true $P(DLT) \geq 33\%$ on study (II)
3. Average proportion of patients receiving a dose with true $P(DLT) < 16\%$ on study (III)
4. Probability of recommending a target dose as the MTD (correct final decision) (IV)
5. Probability of recommending a dose with true $P(DLT) \geq 33\%$ as the MTD (patient risk) (V)
6. Probability of recommending a dose with true $P(DLT) < 16\%$ as the MTD (VI)

Simulation Results

Table 31 below summarizes the simulated operating characteristics of the model for the 4 different scenarios studied, additionally showing the percentage of trials stopped before declaring MTD when all doses were considered too toxic.

Table 31 Results

Scenario	Metric						Stopped	AveN
	I	II	III	IV	V	VI		
1	39.6	0	60.4	81.7	0	17.0	1.3	26.4
2	45.2	12.1	42.7	71.1	14.8	12.4	1.7	26.3
3	29.9	0	70.1	74.2	0	24.7	1.1	25.7
4	0.0	100.0	0.0	0.0	1.0	0.0	99.0	5.4

The simulated operating characteristics presented show that the model performs well under the hypothetical scenarios investigated.

The probability that the identified MTD falls within the target interval (metric IV) is more than 70% for scenarios 1, 2 and 3, showing good targeting of MTD. For scenario 4, because the true DLT rates for all dose levels are greater than 50%, none of the trials identify the MTD falling within the target interval.

In scenario 1 and 2, none of the provisional dose levels have DLT rates ≥ 0.33 . Therefore, the probability of identifying a dose with $P(DLT) \geq 0.33$ as MTD (metric V) is 0. For scenario 3, there is 14.8% chance that the identified MTD with $P(DLT) \geq 0.33$, which is slightly higher. However, comparing to 3+3 design, chances are 23.2% that the identified MTD is overly toxic.

The percentage of trials that were stopped before declaring MTD in scenario 1, 2, and 3 is relatively low, under 2%. There is 99% chance that the trial stops for being overly toxic.

On average, trials enroll 25-27 subjects in scenario 1, 2, and 3. For scenario 4, an average of 5.4 subjects are enrolled. However, this is considered to be overestimated because the simulation does not allow for dose escalation decisions taken outside of the model. In practice, if 2 subjects experiencing a DLT at a previously untested dose, enrollment to that cohort will stop, and the next cohort will be opened at a lower dose level that satisfies the

EWOC criteria. In conclusion, the simulations performed illustrate that model has reasonable operating characteristics. The probability of identifying a dose in the target toxicity interval is high (except for scenario 4) and with $P(DLT) \geq 0.33$ as MTD (metric V) is low for most scenarios.

5 13. PERMITTED MEDICATION TO BE USED WITH CAUTION

In general, the use of any concomitant medication deemed necessary for the care of the participant is permitted in this study, except as specifically prohibited below. Concomitant administration of study treatments could result in DDIs that could potentially lead to reduced activity or enhanced toxicity of the concomitant medications and/or AL-102. Please note that all
10 lists in this section are not comprehensive. Please refer to regular update online sources and the label of the concomitant drug to decide whether a drug is permitted (with caution) or prohibited based on the prohibited Medications section. In case of doubt, please contact the medical monitor with any questions.

The list of CYP3A4, P-gp and BCRP substrates and list of CYP3A4, P-gp and BCRP
15 inhibitors / inducers was compiled from the University of Washington's Drug Interaction Database (updated April 2020). This list is only meant to be used as a guidance.

Table 32 List of CYP3A4, P-gp and BCRP substrates, inhibitors and inducers to be used with caution

Category	Drug name
CYP3A4 substrates which are known or potential auto-perpetrators	clarithromycin, conivaptan, encorafenib, erythromycin, diltiazem, mifepriston, ribociclib, telithromycin, troleandomycin, verapamil
Strong CYP3A inhibitors	ceritinib, clarithromycin, conivaptan, grapefruit juice (citrus paradisi fruit juice, 240 mL TID), idealisib, itraconazole, ketoconazole, mibefradil, mifepristone, nefazodone, posaconazole, ribociclib, telithromycin, troleandomycin, voriconazole
Strong CYP3A4 inducers	apalutamide, avasimibe ¹ , carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifapentine, rifampin (rifampicin), St John's wort (<i>Hypericum perforatum</i>) ¹

Category	Drug name
P-gp inhibitors	alogliptin, amiodarone, azithromycin, canagliflozin, captopril, carvedilol, clarithromycin, clopidogrel, conivaptan, cremophor EL and RH40, curcumin, daclatasvir, diltiazem, dronedarone, eliglustat, erythromycin, felodipine, fluvoxamine, fostamatinib, ginkgo (<i>Ginkgo biloba</i>) ¹ , green tea ¹ , indinavir, isavuconazole, itraconazole, ivacaftor, ketoconazole, lapatinib, lopinavir, mibefradil, milk thistle (<i>silymarin, silibinin</i>) ¹ , mirabegron, nelfinavir, nifedipine, nitrendipine, ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), paroxetine, propafenone, quercetin, quinidine, quinine, ranolazine, rifampicin, ritonavir, rolapitant, saquinavir, <i>Schisandra chinensis</i> extract (wuweizi) ¹ , simeprevir, St. John's wort extract (<i>Hypericum perforatum</i>) ¹ , survorexant, talinolol, telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan, valsopodar, vandetanib, velpatasvir, verapami, voclosporin, vorapaxar
P-gp inducers	carbamazepine, danshen (<i>Salvia miltiorrhiza</i>) ¹ , efavirenz, genistein, phenytoin, quercetin, rifampin, St. John's wort extract (<i>Hypericum perforatum</i>) ¹ , garlic extract ¹
BCRP inhibitors	abacavir, amprenavir, atazanavir, atorvastatin, curcumin, cyclosporine, daclatasvir, delavirdine, efavirenz, , elbasvir, eltrombopag, elvitegravir, erlotinib, fluvastatin, fostamatinib, fumitremorgin, gefitinib, grazoprevir, itraconazole, lapatinib, ledipasvir, lopinavir, nelfinavir, nilotinib, pantoprazole, paritepravir, pitavastatin, rosuvastatin, saquinavir, simvastatin, sulfasalazine, tipranavir, velpatasvir, venetoclax

This list was compiled from the University of Washington's Drug Interaction Database (updated April 2020)

¹ herbal product

14. EXAMPLES

14.1. Example 1: Identification of BSBM3

BCMA is a cell surface receptor expressed on plasma cells, as well as other B-cell malignancies, particularly multiple myeloma. For effective pharmaceutical development, it is highly desirable to have an antibody that is cross-reactive with both human antigens as well as the corresponding antigen in a model non-human primate species, such as cynomolgus macaque, for the purpose of non-clinical pharmacokinetic and toxicology studies.

To identify antibodies that were cross-reactive with both human and cynomolgus BCMA, a naïve phage library containing human antibody fragments was subject to four rounds of panning against recombinant human and cynomolgus BCMA antigens. Approximately 400 single phage colonies were picked from the fourth round panning and nine unique clones were

chosen to be amplified and rescued as phage for phage ELISA. The clones were analyzed for their affinity to human and cyno BCMA.

- One of the clones was subject to affinity maturation in the form of yeast surface scFvs. After multiple rounds of screening affinity matured anti-BCMA pools were cloned into a
- 5 heterodimeric bispecific antibody format (FIG. 1), expressed in HEK 293 cells and tested for the ability to bind BCMA on tumor cells and the ability to activate T-cells in a target-dependent fashion using a Jurkat NFAT luciferase (JNL) reporter assay.

From these assays the bispecific binding molecule referred to herein as BSBM3 was identified. The sequences of BSBM3 are shown in Table 32 below:

TABLE 32 BSBM3 Sequences		
Description	SEQ ID NO	Sequence
HC BCMA arm	1	QVQLVESGGGVVQPGRSLRLSCAASGFTVSSYG MHWRQAPGKGLEWVAVISYTGSNKYYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCGGSG YALHDDYYGLDVWGQGLTVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHKPSDTKVDKKVEPKSCDKTHTCPPCPA PPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVK HEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCD VSGFYPSDIAVEWESDGGQPENNYKTPPVLDSDG SFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNH YTQKSLSLSPGK
DNA HC	4	CAAGTGCAGCTCGTGGAGTCTGGAGGGGGAGT CGTGCAGCCTGGACGCTCCCTGAGACTGTCTT GTGCGGCTTCGGGATTCACTGTGTCCAGCTAC GGCATGCATTGGGTCCGCCAAGCACCGGGAAA AGGCCTGGAGTGGGTGGCCGTGATCTCCTACA CCGGCTCAAACAAGTACTACGCCGACAGCGTG AAGGGCCGGTTCACCATTTCAAGGGACAACCTCC AAGAATACCCTGTATCTGCAAATGAACTCGCTG CGGGCAGAGGACACCGCCGTGTACTACTGCGG TGGCTCCGGTTACGCCCTGCACGATGACTACTA CGGGCTCGATGTCTGGGGACAGGGGACGCTCG TGA CTGTGTCTCGGCTAGCACCAAGGGCCCG TCAGTGTTTCCTCTGGCCCCAAGCTCCAAGTCC ACCTCCGGTGGTACAGCCGCGTTGGGATGCTT GGTCAAGGACTACTTTCCGGAACCCGTGACCGT GTCCTGGAACCTCCGGCGCCCTGACTAGCGGAG TGCACACCTTCCCCGCTGTGCTGCAGTCTAGCG GGCTGTATTCCCTCTCGTCCGTGGTCACCGTGC CGTCCTCATCCCTGGGAACCCAGACCTACATTT GCAACGTGAACCACAAGCCGTCAGACACCAAG

TABLE 32 BSBM3 Sequences		
Description	SEQ ID NO	Sequence
		GTGGACAAGAAGGTGGAGCCGAAGTCCTGCGA CAAGACCCATACTTGTCTCCTTGCCCCGCTCC ACCTGTGGCGGGACCTTCCGTGTTCTTTTCCC GCCGAAGCCGAAGGACACTCTGATGATCTCGC GGACTCCCGAAGTCACTTGCGTGGTGGTGGAC GTCAAACACGAAGATCCCGAGGTCAAGTTCAAT TGGTACGTGGACGGGGTGGAAGTCCACAACGC CAAGACTAAGCCGCGCGAGGAAGAGTACAATT CCACTTACCGGGTCTGTCTCGGTGCTGACTGTG CTGCATCAGGACTGGCTGAACGGAAGGAGTA CAAGTGCAAAGTGTGCAACAAGGCCCTGCCTG CACCAATCGAAAAGACCATTAGCAAAGCCAAGG GCCAGCCGAGAGAACCCCAAGTCTACACTCTG CCACCATCCCGCGAAGAAATGACCAAGAACCAA GTGTCGCTGACGTGCGACGTGTCGGGATTCTA CCCGTCCGATATTGCCGTGGAATGGGAGAGCG ACGGCCAACCCGAGAACAACTACAAGACTACCC CCCCCGTCTTGGATTCCGATGGTTCCTTCTTCC TGTA CTCCAAGCTGACCGTGGATAAGTCCCGAT GGGAGCAGGGCGATGTGTTCTCGTGCTCCGTG ATGCATGAAGCCCTGCACAACCACTATACCCAG AAGTCACTGTCTGCTGAGCCCTGGGAAG
LC BCMA arm	2	QSALTQPASVSGSPGQSITISCTGTSSDVGGINY VSWYQQHPGKAPKLMYDVSNRRLRGVSNRFSGS KSGNTASLTISGLQAEDEADYYCSSYTSSSALYVF GSGTKVTVLGQPKAAPSVTLFPPSSEELQANKAT LVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSK QSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG STVEKTVAPTECS
DNA LC	5	CAGTCGGCGCTGACTCAGCCCGCATCCGTGAG CGGTTACACGGGACAGAGCATCAACATTTCTG CACCGGAACCTCAAGCGACGTGGGCGGCTACA ACTACGTGTCCTGGTATCAGCAGCACCCGGGA AAGGCCCCAAAGCTCATGATCTACGACGTGTCC AATAGACTGCGGGGAGTGTCCAACCGGTTCTC GGGAAGCAAATCCGGCAACACTGCTTCCCTGA CCATCAGCGGACTCCAGGCCGAAGATGAGGCC GACTACTACTGCTCATCCTACACGTCCTCTTCG GCGCTTTACGTGTTTCGGGTGCGGGACCAAGGT CACCGTCCTGGGCCAACCTAAGGCGGCGCCCT CAGTGACCCTGTTCCCTCCGTCTGTCTGAAGAAC TCCAGGCCAACAAAGGCCACCCTCGTGTGCCTG ATTCGGACTTCTACCCGGGAGCCGTCACTGTG GCCTGGAAGGCCGACAGCAGCCAGTGAAGGC CGGCGTGGAAGTACCACCCCGTCCAAGCAGT CCAACAATAAGTACGCAGCCAGCTCCTACCTGT CCCTGACCCCGAACAATGGAAGTCACACAGAT CCTACTCCTGTCAAGTCACCCACGAGGGCAGC ACTGTCGAAAAGACCGTGGCACCGACTGAGTG CTCG

TABLE 32 BSBM3 Sequences		
Description	SEQ ID NO	Sequence
CD3 arm	3	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYA MNWRQAPGKGLEWVGRIRSKANNYATYYADSV KGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVR HGNFGDSYVSWFAYWGQGTLLTVSSGKPGSGK PGSGKPGSGKPGSQAVVTQEPSLTVSPGGTVTL TCGSSTGAVTTSNYANWVQKPGKSPRGLIGGT NKRAPGVPARFSGSLLGGKAALTISGAQPEDEAD YYCALWYSNHWVFGGGTKLTVLEPKSSDKTHTC PPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV VVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREQMTKNQV KLTCLVKGFYPSDIAVEWESNGQPENNYKTPPV LDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHE ALHNHYTQKSLSLSPGK
DNA CD3	6	GAAGTGCAGCTTGTGGAGTCCGGGGGAGGATT GGTCCAACCCGGTGGCTCGCTGAGGCTGAGTT GCGCCGCTTCGGGGTTTACCTTCAGCACCTAC GCTATGAACTGGGTCAGACAGGCGCCTGGAAA GGGTTTGGAGTGGGTCGGACGCATCCGGTCCA AGGCCAACAACTACGCGACTTACTATGCCGACT CCGTCAAGGGACGGTTCACCATCTCCCGGGAC GACAGCAAGAACACCCTGTACCTCCAAATGAAC TCCCTTCGGGCCGAAGATACCGCCGTGTACTAC TGCGTGAGACACGGCAACTTCGGCGACTCCTA CGTGTCTTGGTTTGCCTACTGGGGCCAGGGTA CTCTCGTGACCGTGTCATCAGGAAAGCCAGGCT CGGGGAAGCCTGGCTCCGGAAAGCCTGGGAG CGGAAAGCCGGGATCGCAGGCTGTGGTCACCC AGGAACCCTCCCTGACTGTGTCCCCGGGAGGA ACCGTGACACTGACTTGTGGCAGCTCCACCGG AGCCGTGACCACCTCCAACCTACGCCAACTGGG TGCAGCAAAAGCCAGGAAAGTCCCCTAGGGGG CTGATCGGTGGCAGCAACAAGCGGGCACCTGG AGTGCCTGCCCCGATTCTCGGGTAGCCTGCTGG GGGAAAAGCCGCCCTGACCATTTCGGGCGCT CAGCCAGAGGACGAAGCCGACTATTACTGCGC ACTCTGGTACTCCAACCACTGGGTGTTCCGGTGG AGGCACCAAGCTGACCGTGCTGGAGCCAAAGT CAAGCGACAAAACCTCACACTTGCCCTCCTTGTC CGGCTCCTCCTGTGGCTGGTCCCTCCGTGTTT CTTTCCCGCCGAAGCCGAAGGACACCCTCAT GATTTCCCGGACGCCCGAAGTCACTTGTGTGGT GGTCGATGTGAAGCATGAGGACCCCGAAGTGA AGTTCAATTGGTACGTGGATGGCGTGGAGGTC CACAACGCCAAGACCAAGCCGCGCGAAGAACA GTACAACAGCACCTACCGCGTCGTGAGCGTGC TCACCGTGCTCCACCAAGATTGGCTGAACGGAA AGGAGTACAAGTGCAAAGTGTCCAACAAGGCC CTTCCTGCACCTATTGAAAAGACTATTAGCAAG GCCAAGGGACAGCCCCGCGAACCTCAAGTGTA CACTCTGCCGCCGTCCAGAGAGCAGATGACCA

TABLE 32 BSBM3 Sequences		
Description	SEQ ID NO	Sequence
		AAAACCAGGTCAAGCTCACTTGTCTCGTGAAGG GCTTCTACCCGTCCGATATCGCGGTGCAATGG GAGTCAAACGGCCAGCCCGAGAACAACACTACAA GACTACCCACCGGTGCTTGACTCCGACGGTT CGTTCTTTCTGTACTCCAAGCTGACCGTGGACA AGTCCCGGTGGCAGCAAGGGAATGTGTTTCAGC TGCTCCGTGATGCACGAAGCCCTGCATAACCAC TACACCCAGAAGTCGCTCAGCCTGTCCCCTGGA AAA

The activity of BSBM3 was compared to that of ch2B4_C29, a BCMA-CD3 bispecific antibody in development for the treatment of multiple myeloma (see, WO2016/0166629).

- 5 Preliminary data with bivalent BSBM3 and h2B4_C29 from KMS11 and PBMC/T cell co-culture studies indicate that bivalent BSBM3 mediates lower levels of cytokine induction than h2B4_C29 (data not shown), suggesting that patients treated with BSBM3 may have a reduced risk of cytokine release syndrome compared to patients treated with h2B4_C29. Preliminary data also indicates that T cells activated by h2B4_C29 in the presence of KMS11 cells mediate more TCR downregulation than T cells activated by bivalent BSBM3 (data not shown),
- 10 suggesting that BSBM3 may exhibit more sustained anti-cancer activity than h2B4_C29. Further, in a KMS11 xenograft model, some preliminary data suggests that BSBM3 (as well as h2B4_C29) has greater anti-tumor activity compared to BCMA-CD3 bispecific molecules from EngMab and Janssen.

14.2. Example 2: Characteristics of BSBM3

- 15 BSBM3 is a bispecific antibody that engages both BCMA and CD3, resulting in the recruitment of cytotoxic T cells that target BCMA-positive MM cells. BSBM3 has an IgG like serum half-life that may enable less frequent dosing relative to smaller format BiTE or dual affinity re-targeting Antibody (DART) antibodies. BSBM3 was produced in Chinese hamster ovary (CHO) cells and belongs to the IgG1 isotype subclass. As shown in FIG. 1, BSBM3 has a
- 20 Fab domain targeting BCMA, a single-chain Fv (scFv) domain targeting CD3, and the Fc domain confers IgG-like *in vivo* persistence due to unmodified FcRn (neonatal Fc receptor) affinity. The Fc domain of BSBM3 contains substitutions that ablate binding to human Fcγ receptors and reduce the risk of non-selective T cell activation via FcR (Fc receptor)-mediated crosslinking. Its affinity to BCMA and CD3 has been summarized in Table 33. Binding of
- 25 multiple molecules of BSBM3 simultaneously with BCMA on multiple myeloma (MM) cells and the CD3 subunit of the T cell receptor (TCR) complex on T cells leads to TCR crosslinking and formation of a cytolytic immune synapse, resulting in activation of T cells and specific lysis of MM cells.

TABLE 33		
Antigen	Average KD (M)	Standard Deviation (M)
Human BCMA-Fc	2.01E-10	2.40E-11
Cyno BCMA-Fc	1.29E-09	1.79E-10
Mouse BCMA-Fc	1.15E-09	8.00E-11
Human CD3-biotin	8.78E-09	3.83E-09

Data shown as mean and SD from three biological replicates.

14.3. Example 3: Non-clinical pharmacology (*in vitro*)

The activity of BSBM3 was characterized in an *in vitro* co-culture system with a BCMA+ myeloma cell line KMS11 and healthy donor T cells. BSBM3 induced T cell proliferation and cytokine secretion at concentrations ≥ 1 nM (**FIG. 2**). Consistently, BSBM3 mediated potent redirected T cell cytotoxicity (RTCC) on KMS11 in a concentration-dependent manner (**FIG. 2**). In contrast, a non-targeting control antibody NT-CD3 (with the same anti-CD3 scFv but a non-targeting Fab instead of the anti-BCMA Fab) did not induce T cell proliferation or significant killing of KMS11 cells, indicating that specific binding to BCMA on the tumor cells is required for T cell activation and cytotoxicity. These data suggest that BSBM3 can potently and specifically activate T cells in the presence of BCMA+ cells, resulting in specific killing of the target cells.

In order to identify the *in vitro* assay with the most sensitive readout for the activity of BSBM3, the EC30 values were calculated from the different assays, each performed with nine biological replicates. (T-cells from three healthy donors were tested individually each repeated with three independent experiments; **FIG. 3**). The redirected T-cell cytotoxicity (RTCC) assay which detects specific lysis of MM cells showed the most sensitive and reproducible EC30 values. Therefore, the minimum anticipated biological effect level (MABEL) informing the starting dose was calculated based on EC30 values from RTCC assays.

BCMA has been shown to undergo protease cleavage within its transmembrane domain by γ -secretase, leading to shedding of its extracellular domain as a soluble factor (from here on referred to as soluble BCMA) which serves as a decoy to neutralize its ligand APRIL (Laurent 2015). Average serum levels of soluble BCMA have been reported to be 39 ng/mL in healthy subjects, 89 ng/mL in smoldering myeloma subjects, and 506 ng/mL in newly diagnosed MM subjects (Ghermezi 2017). Soluble BCMA in the blood and bone marrow of subjects has the potential to bind to and interfere with the activity of BSBM3. As expected, in the presence of 30, 100, or 300 ng/mL soluble BCMA, the EC30 for BSBM3 increased by 6, 15, and 41-fold respectively (**FIG. 4**). Because 93% of subjects with active and untreated MM have higher than 107.6 ng/mL shed BCMA in their serum (Ghermezi *et al.*, 2017, Haematologica 102(4):785-795), the RTCC assays containing 100 ng/mL soluble BCMA likely better represent the activity of BSBM3 in subjects. Therefore, the EC30 of 0.753 ng/mL (with 100 ng/mL soluble BCMA)

was taken into consideration when calculating the starting dose using a MABEL approach. This is consistent with the approach described by Saber *et al.*, 2017, Regul Toxicol Pharmacol; 90:144-152 for CD3-directed bi-specific antibodies.

14.4. Example 4: Non-clinical pharmacology (in vivo)

5 The in vivo activity of BSBM3 was evaluated using the KMS11 xenograft model in immunocompromised NSG mice that had been adoptively transferred with human PBMCs from healthy donors (**FIG. 5**). KMS11 cells were engineered to overexpress luciferase, which then enabled tumor burden measurement by bioluminescence intensity (BLI). Mice treated with BSBM3 at doses ≥ 0.3 mg/kg showed robust tumor rejection in three independent experiments
10 with PBMCs from two different healthy donors separately (data).

The adoptively transferred model with KMS11 xenograft provided support to the mechanism of action for BSBM3. However, it likely over predicts the anti-MM activity because the adoptively transferred human T cells are hyperactive as indicated by dramatically higher expression of activation markers compared to T cells in donor PBMCs upon isolation (data
15 shown; Ali *et al.*, 2012, PLoS ONE; 7(8): e44219). Therefore the doses that demonstrated anti-MM activity of BSBM3 in this model are not directly translatable to subjects.

14.5. Example 5: Non-clinical pharmacokinetics and metabolism

To investigate the pharmacokinetics (PK) of BSBM3 in a non-binding species, NSG mouse PK studies were performed with and without human peripheral blood mononuclear cells
20 (PBMC). Concentration-time plots showed bi-exponential decline in serum levels, as expected for a monoclonal antibody in non-binding species. In NSG mice humanized with human PBMCs, exposure as measured by AUClast was lower than in PBMC naïve mice. At the last time points, non-linear elimination became apparent indicating expected target mediated drug disposition (TMDD).

25 BSBM3 binds to both targets (BCMA and CD3) in cynomolgus monkeys, therefore, the toxicokinetic profiles of BSBM3 were investigated in a single dose non-GLP toxicology study (data not shown), and a 4-week GLP toxicology study (data not shown). From the single-dose study, it was determined that exposure to BSBM3, as measured by AUClast increased in a dose proportional manner over the tested doses of 0.3, 1 and 3 mg/kg. Of the five animals
30 dosed, one animal (0.3 mg/kg dose), was confirmed to have anti-drug antibodies (ADA).

In the 4-week cynomolgus monkey GLP toxicology study, animals received 5 weekly i.v. injections of BSBM3 at 1, 3 and 10 mg/kg. After i.v. injection, the maximum exposure to BSBM3 was observed from 0.667 to 4.17 hr post dose, the first time points post-dose. Exposure to BSBM3 as measured by Cmax and AUC0-tau (tau=7 days), increased in an approximately
35 dose-proportional manner over the dose range 1 to 10 mg/kg and was similar in both genders.

Accumulation was approximately 1.5 to 1.9-fold (based on AUC_{0-tau}) after 4 weeks of i.v. dosing at all dose levels. No significant gender differences were observed. ADA were detected on Day 28 (1 of 24 treated animals, 1 mg/kg dose) in the main part of the study. During the 6-week recovery part of the study, ADA were detected on Day 57 (1 of 6 treated animals, 3 mg/kg dose) and Day 71 (2 of 6 treated animals, control group). The data suggest that there was likely no significant impact of ADA on TK. ADA were not detected in control animals.

14.6. Example 6: Non-clinical toxicology

The safety of BSBM3 was investigated in *in vitro* and *in vivo* studies. *In vivo* studies were conducted in cynomolgus monkeys, which was identified as the pharmacologically relevant species for BSBM3.

Results of safety pharmacology studies indicate the risk of BSBM3 to vital functions of the central nervous system (CNS), respiratory, and cardiovascular system is low. In general, findings from *in vivo* studies were consistent with BSBM3-related expected pharmacology of peripheral blood, bone marrow and tissue B cell and plasma cell decreases as well as post-dose acute increases of select serum cytokines and more persistent blood and tissue T-cell activation. Depletion of lymphocytes in the gut-associated lymphoid tissue (GALT), lymph nodes and spleen (B cell regions) were noted at all BSBM3 dose levels in the GLP study (Study No 1870097). During the recovery phase, lymphocyte hyperplasia in these organs was consistent with the regenerative process. In addition, mixed cell immuno-inflammatory lesions were observed in various organs (i.e. gastrointestinal tract (GIT), liver, spleen, heart, kidney, lung) and sometimes associated with infectious agents.

The highest non-severely toxic dose (HNSTD) in the GLP study was identified as 1 mg/kg.

14.7. Example 7: Clinical Study

A clinical trial according to the schema shown in FIG. 6 is conducted to determine the safety and efficacy of BSBM3 in subjects with multiple myeloma who have received two or more standard of care (SoC) lines of therapy including an IMiD (e.g. lenalidomide or pomalidomide), a proteasome inhibitor (e.g. bortezomib, carfilzomib), and an anti-CD38 agent (e.g. daratumumab) and are relapsed and/or refractory to or intolerant of each regimen.

Inclusion Criteria

Subjects included in the trial have a confirmed diagnosis of multiple myeloma and have received two or more standard of care (SoC) regimens including an IMiD (e.g. lenalidomide or pomalidomide), a proteasome inhibitor (e.g. bortezomib, carfilzomib), and an anti-CD38 agent (e.g. daratumumab), if available, and are relapsed and/or refractory to or intolerant of each

regimen, with documented evidence of disease progression (IMWG criteria) and must not be eligible for treatment with other regimens known to provide clinical benefit, as determined by the investigator (subjects who have received a prior autologous bone marrow transplant a BCMA CAR-T, or BCMA-ADC therapy and otherwise meet the inclusion criteria are eligible for this study; have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 at screening; and have measurable disease defined by at least 1 of the following 3 measurements: (i) serum M-protein ≥ 1.0 g/dL; (ii) urine M-protein ≥ 200 mg/24 hours; or (iii) serum free light chain (sFLC) > 100 mg/L of involved FLC.

Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study: radiotherapy within 14 days before the first dose of study drug except localized radiation therapy for lytic bone lesions or plasmacytomas; major surgery within 2 weeks before the first dose of study drug; use of systemic chronic steroid therapy (≥ 10 mg /day of prednisone or equivalent), or any immunosuppressive therapy within 7 days of first dose of study treatment (topical, inhaled, nasal, or ophthalmic steroids are allowed); prior use of BCMAxCD3 bispecific therapies; subjects receiving systemic treatment with any immunosuppressive medication (other than steroids as described above); history of severe hypersensitivity reactions to any ingredient of study drug(s) and other mAbs and/or their excipients; subjects with toxicity to prior BCMA targeted agents; malignant disease, other than that being treated in this study.

(Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.); Active, known or suspected autoimmune disease other than subjects with vitiligo, residual hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic treatment or conditions not expected to recur; subjects who are currently receiving treatment with a prohibited medication that cannot be discontinued at least one week prior to the start of treatment; subjects with Grade ≥ 2 neuropathy, and residual toxic effects from previous therapy must have resolved to Grade ≤ 1 or baseline; subjects with plasma cell leukemia and other plasmacytoid disorders, other than MM; any of the following clinical laboratory results: (i) absolute neutrophil count (ANC) $< 1,000/\text{mm}^3$ without growth factor support within 7 days prior to the start of treatment; (ii) platelet count $< 75,000/\text{mm}^3$ without transfusion support within 7 days prior to the start of treatment; (iii) bilirubin > 1.5 times the upper limit of the normal range (ULN); (iv) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times the ULN; (v) calculated creatinine clearance < 30 ml/min according to Cockcroft-Gault equation; (vi) impaired cardiac function or clinically significant cardiac disease; active infection requiring systemic therapy or other severe infection within 2 weeks before the first dose of study drug; POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy,

monoclonal protein, skin changes); prior allogeneic SCT at any time prior to signing informed consent for the study; human immunodeficiency virus (HIV infection); active Hepatitis B (HBV) or Hepatitis C (HCV) infection; use of any live vaccines against infectious diseases (e.g. influenza, varicella, pneumococcus) within 4 weeks of initiation of study treatment; treatment with cytotoxic or small molecule targeted antineoplastics, or any experimental therapy, within 14-days or 5 half-lives whichever is shorter before the first dose of study treatment; initiation of hematopoietic colony-stimulating growth factors (e.g. G-CSF, M-CSF), thrombopoietin mimetics or erythroid stimulating agents ≤ 2 weeks prior to start of study treatment; intravenous IG infusions given for infection prophylaxis must be discontinued ≥ 28 days prior to start of study treatment; active central nervous system (CNS) involvement by malignancy or presence of symptomatic CNS metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery), or increasing doses of corticosteroids within the 2 weeks prior to the start of study treatment; serious medical or psychiatric illness likely to interfere with participation in this clinical study; pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test; and women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using two effective methods of contraception, including at least one highly effective method, at the time of informed consent, during dosing and for 6 months after the last dose of study drug.

20 **Course of Treatment**

This study consists of a dose escalation part followed by an expansion part.

BSB3 will be initially administered weekly (Q1W). Study drug treatment will continue until a subject experiences unacceptable toxicity, progressive disease as per IMWG or treatment is discontinued at the discretion of the investigator or the patient. Alternative dosing schedules (e.g. Q2W, Q3W, TIW) may be implemented during the study if supported by emerging data including preliminary PK, PD and efficacy findings from this ongoing trial. If clinically significant cytokine release syndrome (CRS) or associated symptoms are observed during dose escalation, the option of a priming dose may be introduced and subsequent dosing schedules modified.

During dose escalation, subjects with relapsed and/or refractory MM will be treated with BSB3 until the MTD/RD is reached. An estimated 21 subjects are required during escalation to define the MTD/RD.

The safety (including the dose-DLT relationship) and tolerability of the study treatment will be assessed, and regimen(s) and dose(s) will be identified for use in the expansion part based on the review of these data. The RD will also be guided by the available information on PK, PD, and preliminary anti-tumor activity. The dose escalation will be guided by an adaptive

Bayesian logistic regression model (BLRM) following the Escalation with Overdose Control (EWOC) principle.

The dose for single agent BSBM3 is proposed based on an integrated assessment of predicted pharmacokinetics, the mechanism of action, in vitro potency (to inform a MABEL dosing approach), the impact of circulating BCMA and in vivo safety in the cynomolgus monkey GLP toxicology study. The starting dose for single agent BSBM3 for subjects is 3 mcg/kg administered as a 2 hour intravenous infusion.

This starting dose for the single agent BSBM3 is supported by the EC50 value (~ 0.07 µg/mL) from the RTCC assay (without added recombinant soluble BCMA) which is believed to represent the most clinically relevant measure of pharmacological activity and is the most sensitive and reproducible assay readout for BSBM3 in vitro.

BSBM3 is found to be safe and well tolerated, and found to have anti-tumor activity.

The phase I starting dose of BSBM3 given in combination with AL-102 is 12 mcg/kg. This dose level is one dose level lower than the 24 mcg/ kg dose level, the highest single agent BSBM3 dose deemed to be tolerated as per EWOC criteria in the ongoing single agent dose escalation.

The Phase I starting dose for AL-102 in combination with BSBM3 for subjects enrolled in this trial is 2 mg twice weekly on consecutive days (2 days on / 5 days off) and is proposed based on available clinical and preclinical data. Firstly, in the phase I dose escalation study of AL-102 in advanced solid tumors patients, both the 2 mg and the 4 mg BIW doses were cleared with no DLTs (2 patients/cohort), whereas 2 DLTs/ 6 evaluable patients (1 Grade 3 diarrhea and 1 Grade 3 dehydration and anorexia) occurred at the 8 mg BIW dose. Therefore, the proposed starting dose of AL-102 is considered tolerated in an oncology phase 1 population. Additionally, administration of GSIs (AL-102 (Aung et al, 2018) and JSMD194 (Massard et al. 2018)) is associated with GI toxicity in humans and preclinical species, which is characterized by goblet cell hyperplasia. As the intestinal surface epithelium, including goblet cells, is continuously renewed with turnover between 3 to 7 days in humans (Barker, 2014), the 2 days on / 5 days off regimen should give goblet cells time to recover and improve GI tolerability of AL-102. Lastly, preclinical exposure of AL-102 BIW was sufficient to decrease sBCMA in circulation and increase mBCMA density on MM cells. In preclinical studies, we observed dose-dependent response with higher dosed being more efficacious, thus intermittent regimen would allowed exploration of higher daily doses compared to continuous dosing.

The proposed timing of administration of AL-102 with BSBM3 when given in combination is as follows: AL-102 will be given as a single agent on day 1, followed by administration of both AL-102 and BSBM3 on the subsequent day (day 2) every week until permanent discontinuation of study treatment. Modeling of preclinical and clinical data predict

that AL-102 dosed prior to BSBM3 dose (day 1) leads to lower sBCMA and higher BCMA density on surface on myeloma cells than when the two drugs are co-dosed. As inhibition of BCMA cleavage is reversible, analysis of sBCMA following AL-102 administration prior BSBM3 will help to determine the effect of AL-102 on sBCMA, characterize pharmacokinetic/ pharmacodynamic relationship and further optimization of dose and/or dosing regimen.

14.8. Example 8: Effective Dose Range of AL-102 for BCMA Shedding Inhibition

14.8.1. Overview

Gamma secretase inhibitor (GSI), AL-102, was evaluated for its effect on B cell maturation antigen (BCMA) shedding in KMS11 cells in vitro.

14.8.2. Materials and Methods

14.8.2.1. GSI treatment of KMS11 cells

KMS11-Luc cells were cultured in a 96-well round bottomed plate (Corning #3799) at 1.5×10^5 cells per well in a final volume of 200 μ L that included a 12-point, 5-fold serial dilution of AL-102 in RPMI1640 (Gibco #11875-085) supplemented with 20% FBS (Seradigm #1500-500) and L-glutamine (Thermo Fisher #25030-081). The highest starting concentration of AL-102 was 1 μ M. Cells were incubated for 20 hours at 37°C/5% CO₂. Cells were pelleted, supernatant collected for measurement of shed BCMA levels, and cell pellets stained for evaluation of BCMA membrane expression levels.

14.8.2.2. Measurement of shed BCMA levels by ELISA

Soluble BCMA levels in supernatant were determined by ELISA following a vendor supplied protocol (R&D Systems #DY193). Briefly, recombinant human BCMA-Fc protein was included in the kit, and used to generate a standard curve. Collected samples were assayed and sBCMA concentrations extrapolated from the standard curve. Quantified values as determined by the kit were divided by 5.5 to correct for a molecular mass difference between BCMA-Fc fusion protein used in the kit as a standard curve (32,554.6 Da) and the mass of endogenously shed BCMA extra-cellular domain (5,899.3 Da). The results were analyzed using SoftMax Pro v5.4.1 and graphed in GraphPad Prism.

14.8.2.3. Analysis of BCMA membrane expression by Flow cytometry

Cells were pelleted by centrifugation, and supernatants were transferred to a fresh plate and frozen at -80°C for later sBCMA analysis by ELISA. For membrane BCMA analysis, cell pellets were resuspended in 100 μ L BD Stain Buffer containing BSA (BD#554657) and stained with anti-BCMA-PE (Biolegend, clone 19F2 1.25 μ L/test) and Fixable Viability Dye eFluor506 (Thermo Scientific, 1:800 dilution) for 30 minutes at 4°C. Samples were analyzed by flow cytometry on a BD LSR Fortessa instrument. FlowJo v10 software was used for analysis. The anti-BCMA antibody binding capacity (ABC) on KMS11 cells was determined using Quantum Simply Cellular beads (Bangs Laboratories) following a vendor supplied protocol. The ABC is an

estimate of the quantity of receptors per cell. These results were plotted in Graphpad Prism against the concentration of AL-102.

14.8.3. Results

AL-102 treatment led to reduced sBCMA and increased mBCMA density on MM cell line KMS11 *in vitro*. (FIG. 8A) Concentration of sBCMA levels (ng/mL) from the culture supernatants of KMS-11 cells treated for 20 hours with a serial dilution of AL-102 are shown on the left Y-axis. Cell surface mBCMA density is represented by Antibody Binding Capacity (ABC) using anti-BCMA (clone 19F2) on the surface of these AL-102 treated KMS-11 cells is shown on the right Y-axis. EC50 values are calculated by using a sigmoidal, 4-parameter non-linear regression curve fit. Time course of sBCMA and mBCMA levels following the administration of AL-102. (FIG. 8B) NSG mice with established subcutaneous tumors from KMS11 cells were dosed with AL-102 for 5 doses (first dose at 0 hr and last dose at 48 hr). Levels of sBCMA (ng/mL) from the serum at the indicated time points were measured by ELISA (closed circles, left Y-axis) whereas mBCMA levels on tumor cells were measured by flow cytometry and shown as MFI (open squares, right Y-axis)

BSBM3 mediated RTCC activity was assayed in the presence of 8nM AL-102. (FIG. 10) BSBM3 was added at 1:5 serial dilutions across ten points starting from 10 nM. The average RTCC activity (mean+/-SEM) from three independent RTCC assays (using three different healthy donor T cells) were plotted against BSBM3 concentrations in the presence of 8nM AL-102.

14.9. Example 9: AL-102 Impact on BSBM3 Potency

14.9.1. Overview

To evaluate the ability of AL-102 to enhance the activity of BSBM3, a redirected T cell cytotoxicity (RTCC) assay was performed using human T cells and a BCMA-expressing multiple myeloma cell line treated with dose range combinations of BSBM3 and AL-102 in a 10x8 matrix fashion.

14.9.2. Materials and Methods

14.9.2.1. Healthy human T cell isolation

Human T cells were enriched from peripheral blood of three healthy human donors. First, peripheral blood mononuclear cells (PBMCs) were fractionated from donor blood using a Ficoll-
 5 Paque PLUS density gradient (GE Healthcare #17-1440-02) in Leucosep tubes (Greiner #227290) and stored as viable frozen aliquots in liquid nitrogen. PBMC were thawed and Pan T cells were isolated by negative selection according to manufacturer's recommended protocol (Miltenyi #130-096-535). The unlabeled cell fraction, enriched for T cells, was collected by manual magnetic separation on LS columns (Miltenyi #130-042-401). T cells were prepared in T cell
 10 media (TCM) consisting of RPMI-1640 (Gibco #11875-085), 10%FBS (Seradigm #1500-500), 1% Pen/Strep (Life Technologies #15070063), 1% L-glutamine (Thermo Scientific #25030-081), 1% Non-Essential Amino Acids (NEAA) (Life Technologies #11140-050), Sodium Pyruvate (NaPy)(Life Technologies #11360-070), HEPES (Life technologies, Cat # 15630080), 0.1%2-Betamercaptoethanol (2-BME) (Life Technologies, Cat # 21985-023).

15 14.9.2.2. KMS11 multiple myeloma cell line

KMS11 multiple myeloma cell line was cultured in RPMI1640 supplemented with 20% FBS (Gibco #11875-085, Seradigm #1500-500).

14.9.2.3. Re-directed T cell cytotoxicity (RTCC) assay

The target MM cell line KMS11 was transduced to constitutively express luciferase
 20 (KMS11-Luc), and used to measure cell viability/survival. KMS11-Luc cells were pelleted and resuspended in fresh media immediately prior to plating to remove any basal level of shed BCMA that may be present. 7,500 KMS11-Luc target cells in 10 μ L TCM were added to wells of 384-well plates (Corning #3765). 10 μ L of BSBM3 at a concentration of 10nM was serially diluted 5-fold, and 10 μ L of AL-102 at a concentration of 1000nM was serially diluted 5-fold, and dispensed
 25 into corresponding wells of the assay plates. 15,000 T cells were added to corresponding wells of the assay plate in 10 μ L TCM for an E:T of 2:1. The assay was incubated at 37°C/5% CO₂ for 48 hr, followed by measurement of luciferase activity to indicate target cell viability (BrightGlo, Promega #E2650) following manufacturer's protocols. Plates were read on an Envision plate reader. Target cells only (KMS11-Luc) without T cells or antibodies served as control and
 30 represent 100% luciferase activity (100% viability). Data were plotted and analyzed using GraphPad Prism. EC₅₀ values were calculated using sigmoidal, 4-parameter non-linear regression curve fit.

14.9.3. Results

An RTCC assay was set up with three individual T cell donors cultured with KMS11-Luc
 35 cells in the presence of dose response curves of BSBM3 alone or in combination with AL-102. BSBM3 showed a dose dependent effect on KMS11-Luc cell death with EC₅₀ value of 1nM. Combination of BSBM3 with AL-102 increased BSBM3 killing capacity (FIG. 9). AL-102

decreased BSBM3 EC50 values from 1nM to as low as 0.02 nM, which indicates enhanced RTCC activity of BSBM3 in the presence of AL-102. This represents a 50-fold increase in BSBM3 potency. AL-102 at 0.32 nM or lower had minimal effect on BSBM3 potency, at 1.6nM had a moderate effect, and at concentrations of 8nM or higher showed maximum enhancement of

5 BSBM3 potency. These results demonstrated that AL-102 combination with BSBM3 synergistically enhanced the RTCC potency of BSBM3.

WHAT IS CLAIMED IS:

1. A method of treating a subject suffering from multiple myeloma, comprising administering to the subject one or more treatment doses of a B-cell maturation antigen (BCMA) binding molecule and a gamma secretase inhibitor (GSI), wherein the GSI is administered at a dose of about 0.1 mg to about 10 mg for at least once a week.
2. The method of claim 1, wherein the GSI is administered at a dose of about 0.9 mg, 2 mg, 4mg, or 6 mg.
3. The method of claim 1 or 2, wherein GSI is administered twice a week as a first GSI dose and a second GSI dose.
4. The method of claim 3, wherein the first GSI dose and the second GSI dose is administered on two consecutive days.
5. The method of claim 4, wherein the first GSI dose is administered about 24 hours prior to the second GSI dose.
6. The method of any one of claims 3 to 5, wherein after the second GSI dose, the subject is not administered a GSI for at least 5 consecutive days.
7. The method of any one of claims 1 to 6, wherein the first GSI dose is administered to the subject one day before the BCMA binding molecule is administered.
8. The method of any one of claims 1 to 7, wherein the second GSI dose is administered to the subject on the same day as the BCMA binding molecule is administered.
9. The method of any one of claims 1 to 8, wherein the first GSI dose is administered to the subject the day before the BCMA binding molecule is administered and the second GSI dose is administered to the subject on the next day along with the BCMA binding molecule.
10. The method of claim 9, wherein the second GSI dose is administered to the subject about 2 hours prior to the administration of the BCMA binding molecule.
11. The method of any one of claims 1 to 10, wherein the first and/or the second dose of GSI are given as an oral capsule.

12. The method of claim 11, wherein the oral capsule comprises GSi in the amount of about 0.3 mg or about 2.0 mg.

13. The method of any one of claims 1 to 12, wherein the GSi is LY-450139, PF-5212362, BMS-708163, MK-0752, ELN-318463, BMS-299897, LY-411575, DAPT, AL-101 (BMS-906024), AL-102 (BMS-986115), PF-3084014, RO4929097, or LY3039478.

14. The method of any one of claims 1 to 13, wherein the GSi is AL-102 (BMS-986115).

15. The method of any one of claims 1 to 14, wherein the BCMA binding molecule is an antibody, RLT, or CAR-T.

5 16. The method of any one of claims 1 to 15, wherein the BCMA binding molecule is an antibody.

17. The method of claim 16, wherein the BCMA binding molecule is a bispecific antibody.

10 18. The method of claim 17, wherein the bispecific antibody binds to human BCMA and human CD3 and comprises:

 (a) a first polypeptide whose amino acid sequence comprises the amino acid sequence of SEQ ID NO:1;

 (b) a second polypeptide whose amino acid sequence comprises the amino acid sequence of SEQ ID NO:2; and

 (c) a third polypeptide whose amino acid sequence comprises the amino acid sequence of SEQ ID NO:3.

19. The method of any one of claim 1 to 18, wherein the BCMA binding molecule is an bispecific antibody that is dosed at between about 1 µg/kg to 600 µg/kg.

20. The method of claim 19, wherein the BCMA bispecific antibody is dosed at least at 12 µg/kg.

21. The method of any one of claims 1 to 20, wherein the BCMA bispecific antibody is administered to the subject at a dose of about 6 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 0.9 mg.

22. The method of any one of claims 1 to 20, wherein the BCMA bispecific antibody is administered to the subject at a dose of about 12 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 0.9 mg.

23. The method of any one of claims 1 to 20, wherein the BCMA bispecific antibody is administered to the subject at a dose of about 12 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 2 mg.

24. The method of any one of claims 1 to 20, wherein the BCMA bispecific antibody is administered to the subject at a dose of about 24 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 2 mg.

25. The method of any one of claims 1 to 20, wherein the BCMA bispecific antibody is administered to the subject at a dose of about 48 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 2 mg.

26. The method of any one of claims 1 to 20, wherein the BCMA bispecific antibody is administered to the subject at a dose of about 48 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 4 mg.

27. The method of any one of claims 1 to 20, wherein the BCMA bispecific antibody is administered to the subject at a dose of about 96 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 4 mg.

28. The method of any one of claims 1 to 20, wherein the BCMA bispecific antibody is administered to the subject at a dose of about 192 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 4 mg.

29. The method of any one of claims 1 to 20, wherein the BCMA bispecific antibody is administered to the subject at a dose of about 384 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 4 mg.

30. The method of any one of claims 1 to 20, wherein the BCMA bispecific antibody is administered to the subject at a dose of about 384 µg/kg and the first and/or second GSi dose is administered to the subject at a dose of about 6 mg.

31. The method of any one of claims 1 to 15, wherein the BCMA binding molecule is a CAR-T.

32. The method of any one of claims 1 to 15, wherein the BCMA binding molecule is RLT.
33. The method of any one of claims 1 to 32, wherein the method is repeated until the subject is in remission.
34. The method of claim 33, wherein the remission is complete or partial remission.
35. The method of any one of claims 1 to 34, wherein the subject has measurable disease.
36. The method of claim 35, wherein the subject
- (a) has serum M-protein levels of ≥ 1 g / dL;
 - (b) produces urine M-protein levels of ≥ 200 mg / 24 hours; and/or
 - (c) has serum free light chain (sFLC) levels of at least 100 mg / L of involved FLC.
37. The method of any one of claims 1 to 36, wherein the multiple myeloma is relapsed.
38. The method of any one of claims 1 to 37, wherein the multiple myeloma is refractory.
39. The method of any one of claims 1 to 38, wherein the BCMA binding molecule is administered to the subject intravenously.
40. The method of claim 39, wherein the BCMA binding molecule is administered to the subject as an infusion.
41. The method of claim 40, wherein the infusion is over a 1.5 – 3 hour span.
42. The method of claim 41, wherein the infusion is over a 2 hour span.

43. The method of any one of claims 1 to 42, which comprises prior to administering the first treatment dose of the BCMA binding molecule, administering a priming dose of the BCMA binding molecule to the subject.

44. The method of claim 43, wherein the priming dose is less than the first BCMA binding molecule dose.

45. The method of claim 44, wherein the priming dose is equal to the first BCMA binding molecule dose.

46. The method of any one of claims 43 to 45, wherein administration of the priming dose is initiated one week prior to administering the first BCMA binding molecule dose.

47. The method of any one of claims 43 to 46, wherein the priming dose is divided.

48. The method of claim 47, wherein the priming dose is administered over a period of two days.

49. The method of claim 48, wherein less than half the priming dose is administered on the first day and the remainder of the priming dose is administered on the second day.

50. The method of claim 49, wherein about a third of the priming dose is administered on the first day and about two thirds of the priming dose is administered on the second day.

51. The method of any one of claims 1 to 50, further comprising administering to the subject one or more additional therapeutic agents.

52. The method of claim 51, wherein the additional therapeutic agents are antidiarrheals (e.g., loperamide), octreotide, glucocorticoids (e.g., prednisone, cortisone, dexamethasone), emollients, antibiotics, paracetamol, acetaminophen, antihistamines, anti-T cell directed therapy, or any combination thereof.

53. The method of claim 51 or 52, wherein the one or more additional therapeutic agents reduces a side effect of the GSi and/or the BCMA binding molecule.

54. The method of claim 53, wherein the side effect is cytokine release syndrome (CRS).

55. The method of claim 53 or 54, wherein the additional therapeutic agent is a glucocorticoid.

56. The method of claim 55, wherein the glucocorticoid is dexamethasone or methylprednisolone.

57. The method of claim 56, wherein the glucocorticoid is dexamethasone and is administered at a dose of about 8 mg to about 10 mg daily.

58. The method of claim 56, wherein the glucocorticoid is methylprednisolone and is administered at a dose of at least about 2 mg/kg.

59. The method of claim 53 or 54, wherein the additional therapeutic agent is an anti-T cell directed therapy.

60. The method of claim 59, wherein the anti-T cell directed therapy is tocilizumab, canakinumab, or any combination thereof.

61. The method of any one of claims 1 to 60, wherein the subject has been previously treated with at least two prior treatment regimens.

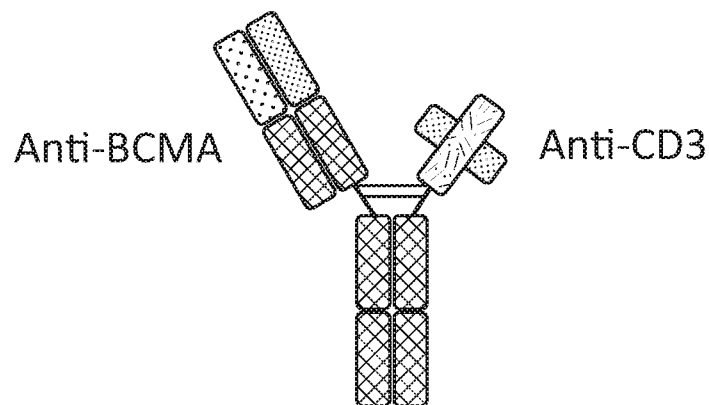


FIG. 1

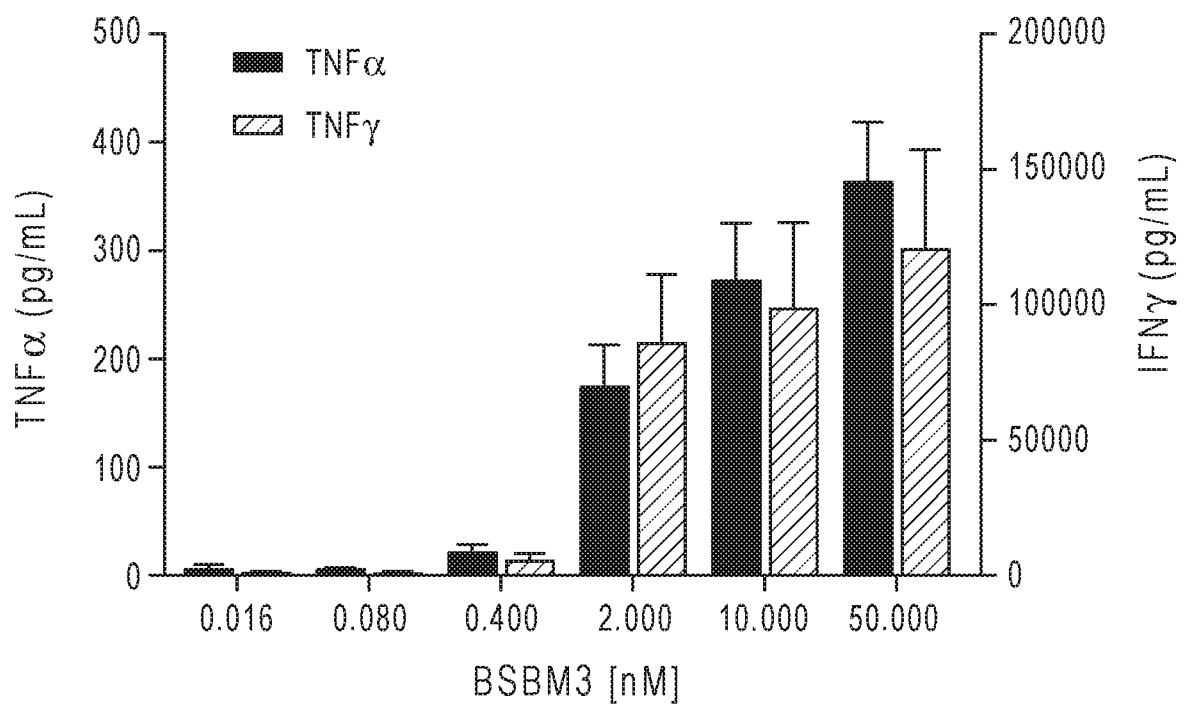


FIG. 2A

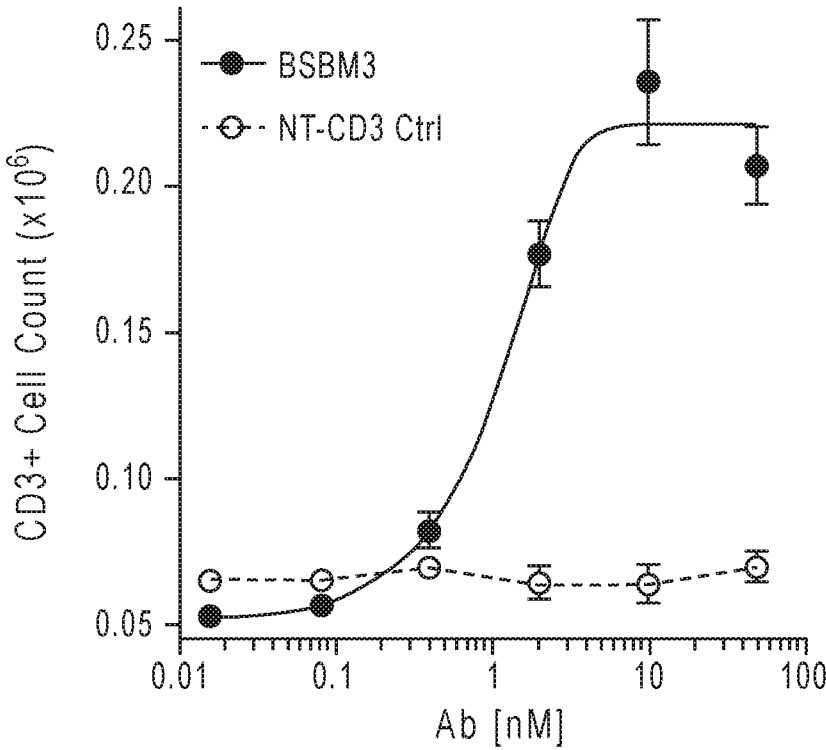


FIG. 2B

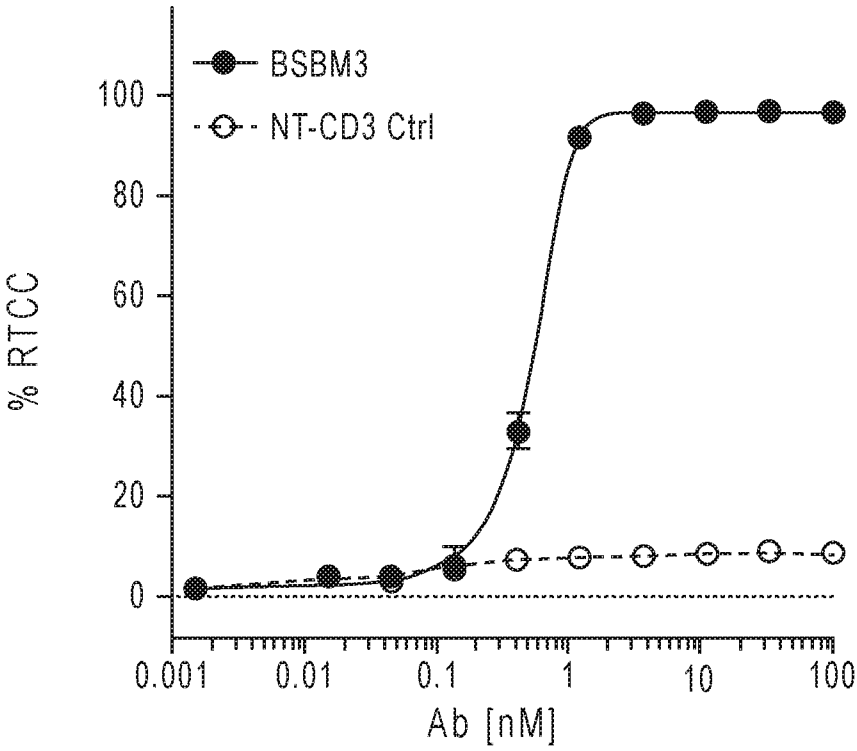


FIG. 2C

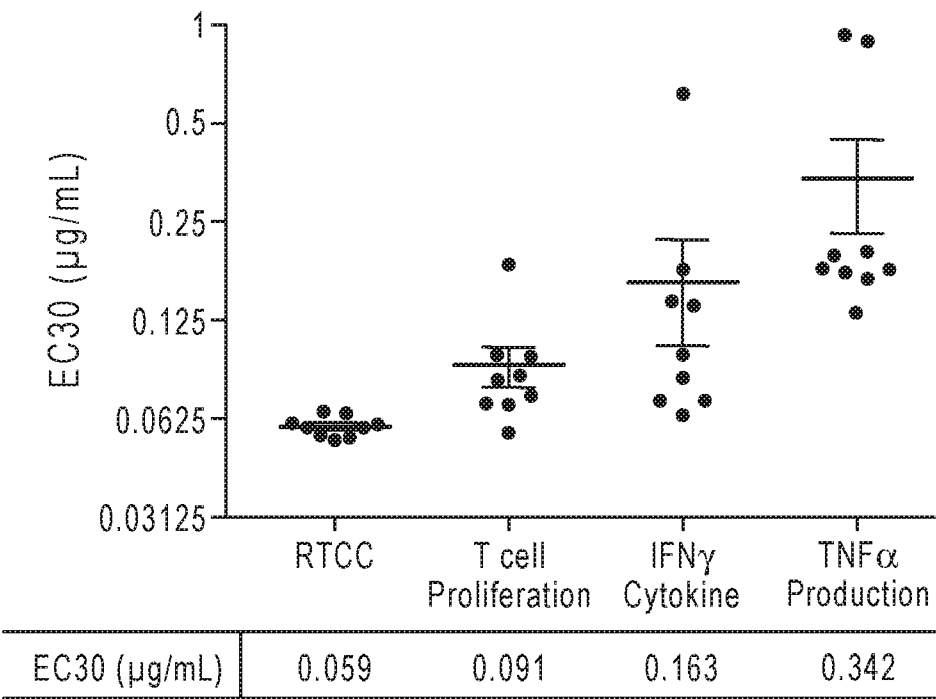


FIG. 3

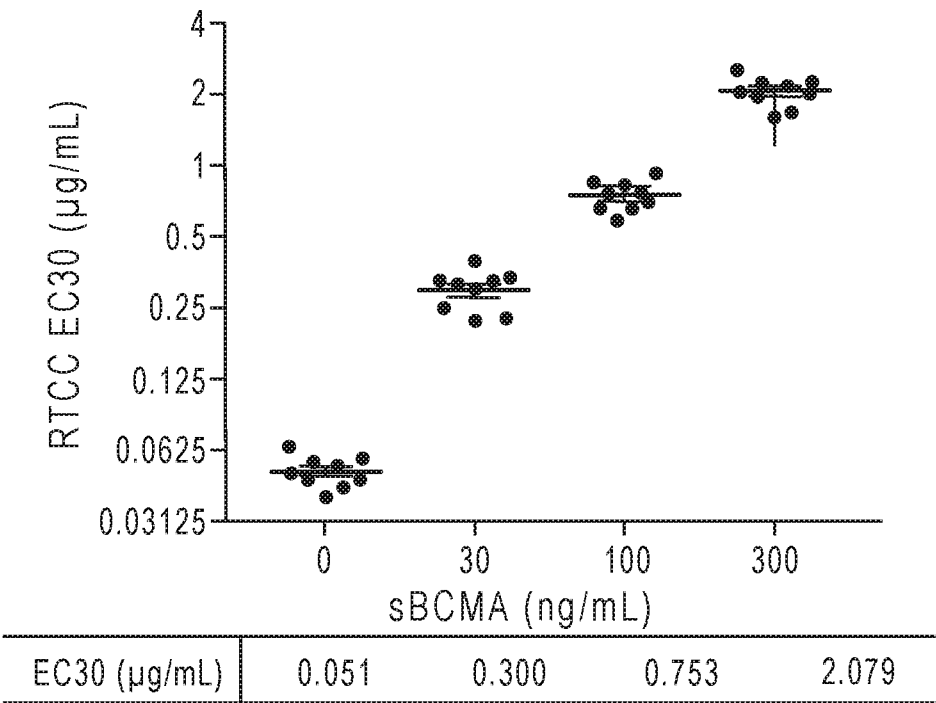
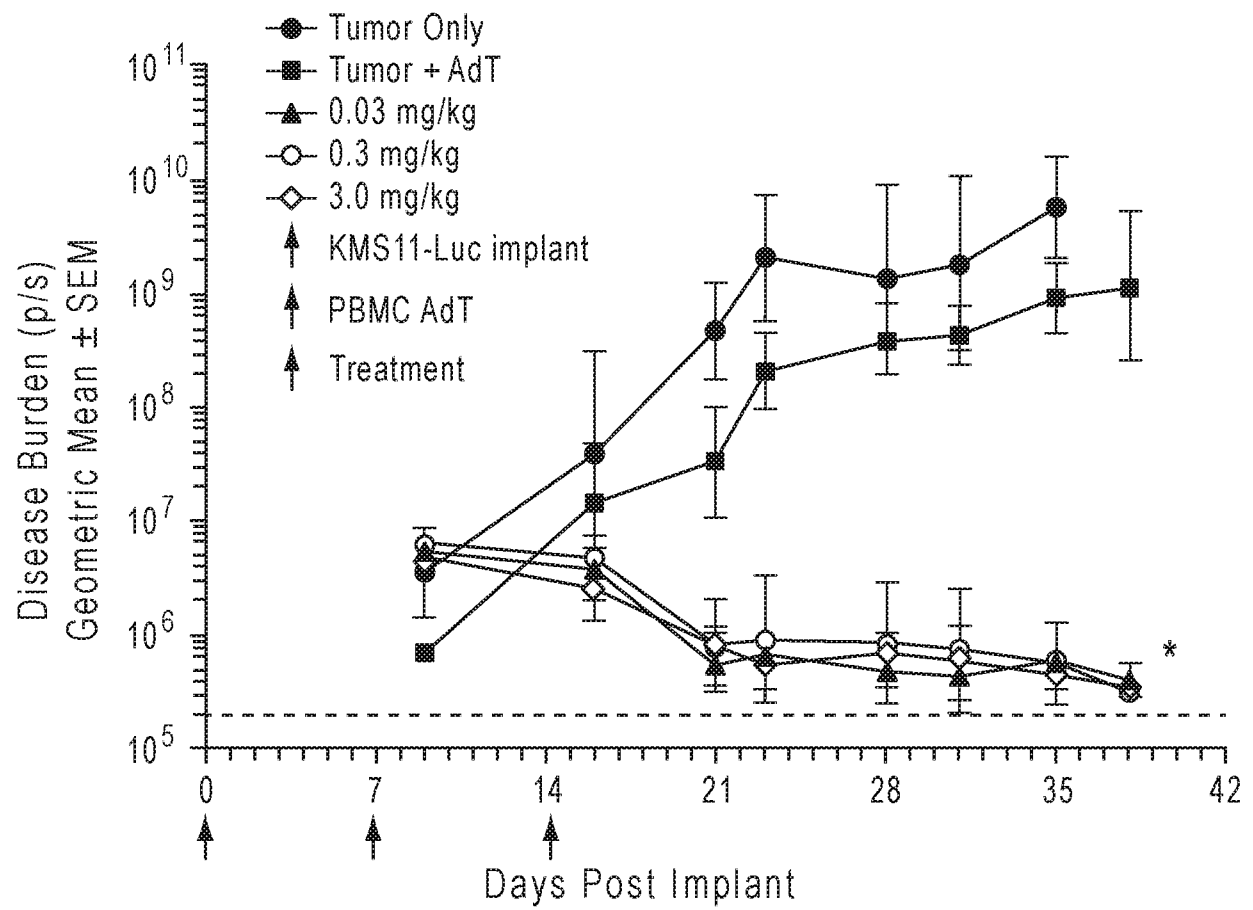


FIG. 4

**FIG. 5**

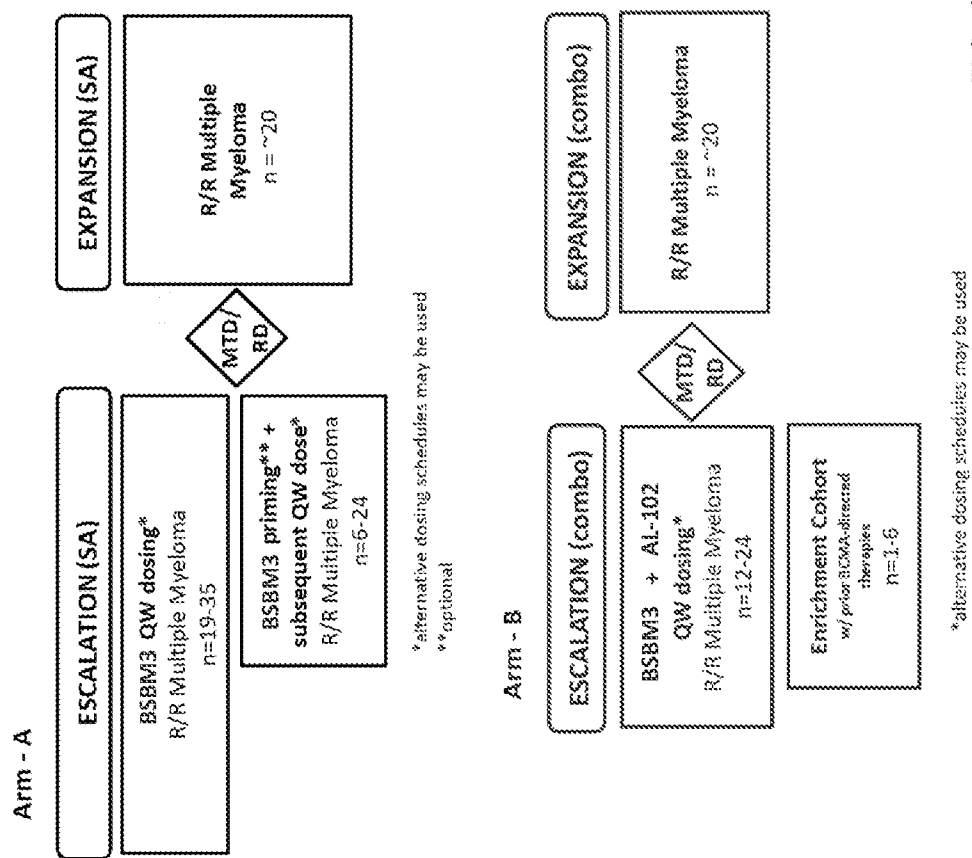
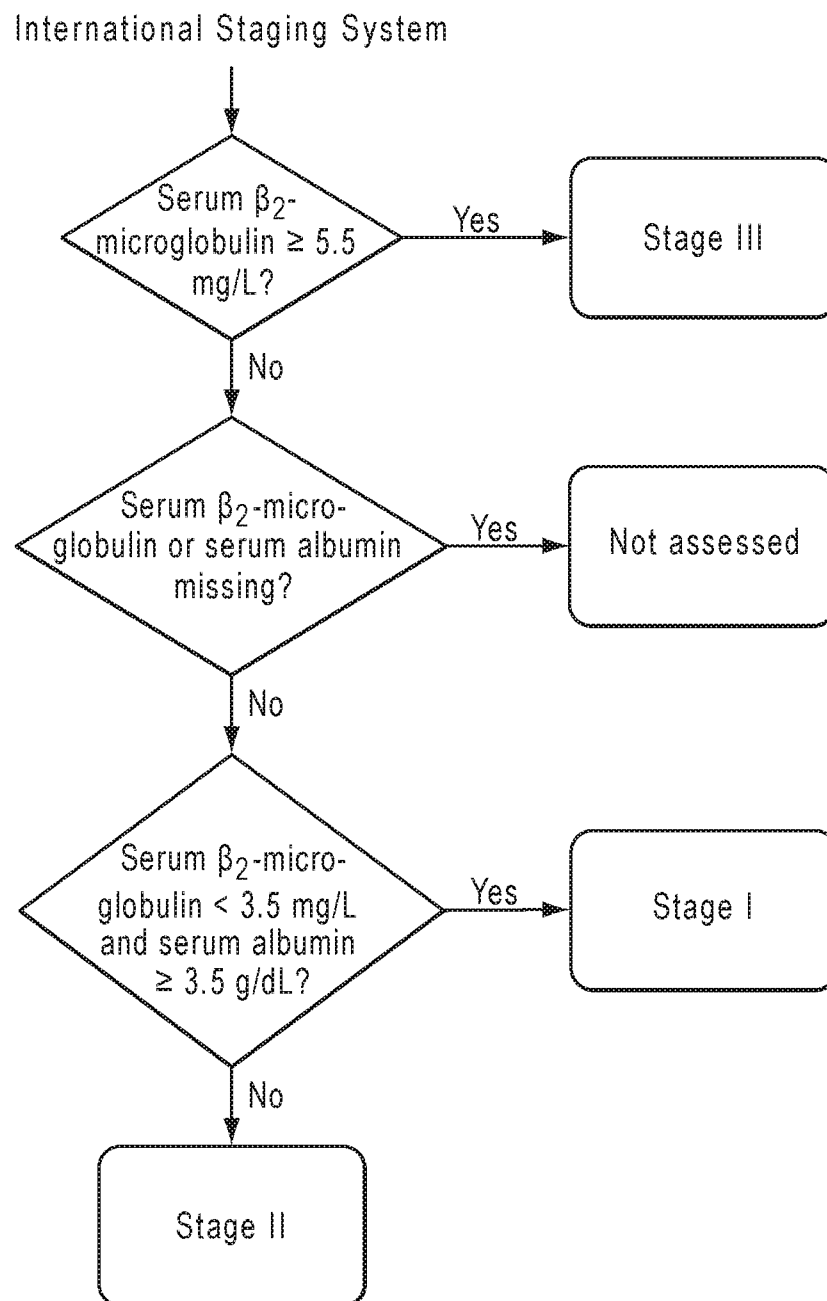


FIG. 6

**FIG. 7**

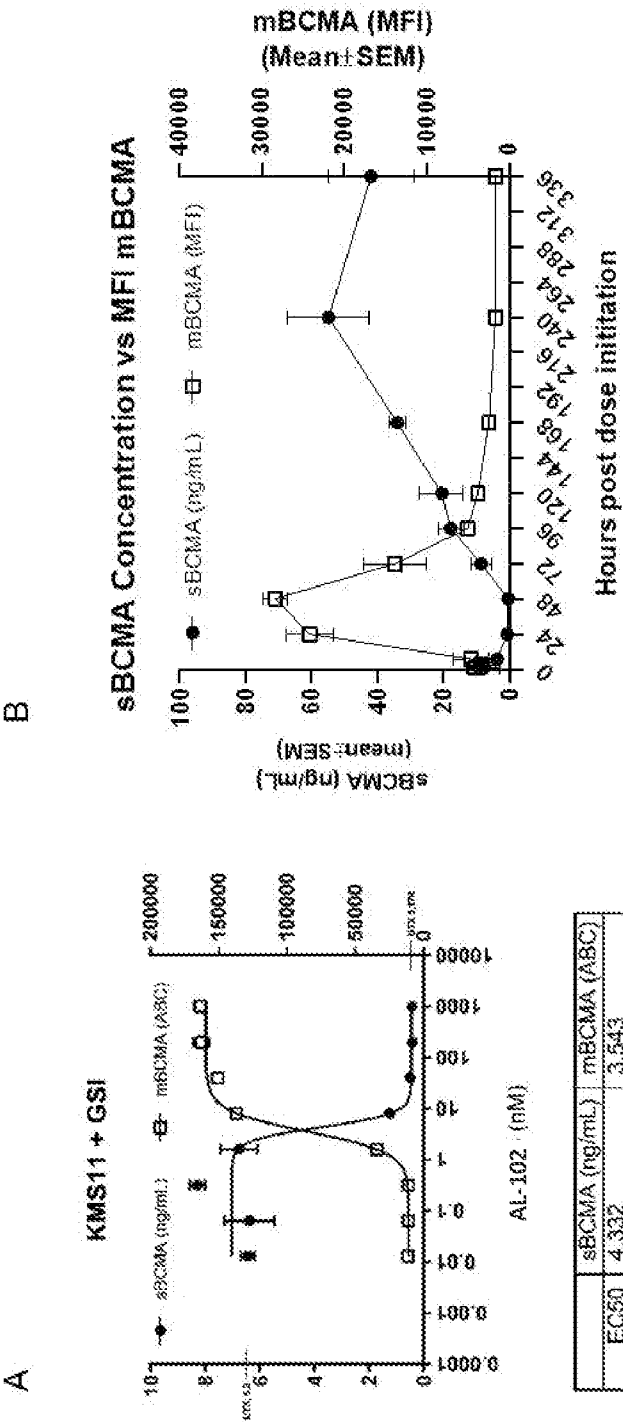


FIG. 8

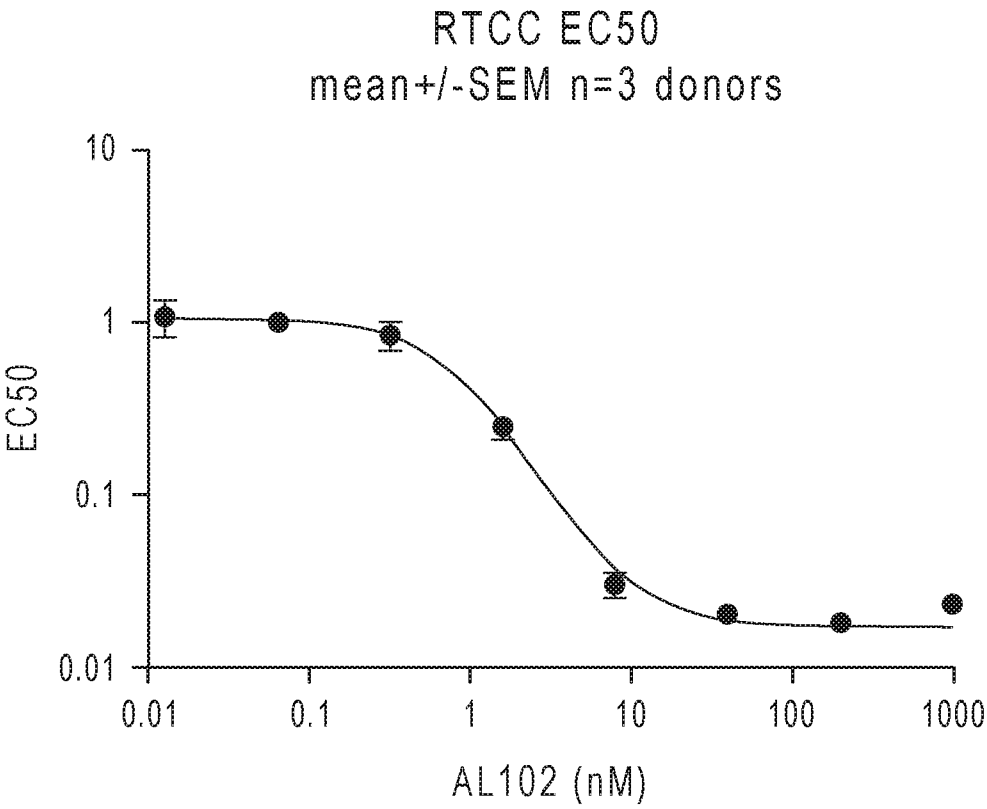


FIG. 9

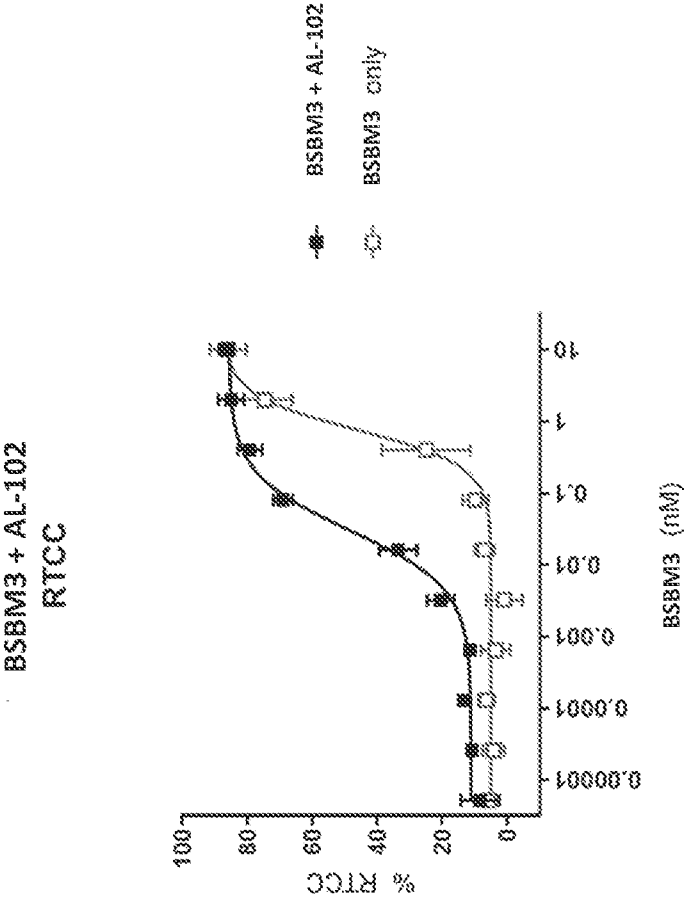


FIG. 10

Provisional dose levels for combination arm

Dose level	Proposed dose BSBM3 *	Proposed dose AL-102	Increment from previous dose
-2	6 mcg/kg	0.9 mg	-100%
-1	12 mcg/kg	0.9 mg	-110%
1	12 mcg/kg	2 mg	(starting dose)
2	24 mcg/kg	2 mg	100%
3	48 mcg/kg	2 mg	100%
4	48 mcg/kg	4 mg	100%
5	96 mcg/kg	4 mg	100%
6	192 mcg/kg	4 mg	100%
7	384 mcg/kg	4 mg	100%
8	384 mcg/kg	6 mg	50%

*It is possible for additional and/or intermediate dose levels to be added during the course of the study.

**Dose level -1 represents a treatment dose level to be implemented in case the starting dose level is not tolerated. No dose reduction below dose level -2 is permitted for this study.

FIG. 11

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/060276

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K47/68 C07K16/28 A61P35/02 ADD. 		
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) A61P A61K C07K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, Sequence Search, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2020/208572 A1 (GLAXOSMITHKLINE IP DEV LTD [GB]; SPRINGWORKS THERAPEUTICS INC [US]) 15 October 2020 (2020-10-15) page 6; examples 2,4 -----	1-61
Y	WO 2018/201051 A1 (NOVARTIS AG [CH]; DALEY MICHAEL [US]) 1 November 2018 (2018-11-01) the whole document ----- -/--	1-61
☒ 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 "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 17 February 2022	Date of mailing of the international search report 10/03/2022	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Scheffzyk, Irmgard	

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2021/060276

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EASTMAN STEPHEN ET AL: "Synergistic Activity of Belantamab Mafodotin (anti-BCMA immuno-conjugate) with PF-03084014 (gamma-secretase inhibitor) in Bcma-Expressing Cancer Cell Lines", BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 134, 13 November 2019 (2019-11-13), page 4401, XP086668823, ISSN: 0006-4971, DOI: 10.1182/BLOOD-2019-123705 the whole document -----	1-61
Y	PONT MARGOT J. ET AL: "Synergistic Activity of Belantamab Mafodotin (anti-BCMA immuno-conjugate) with PF-03084014 (gamma-secretase inhibitor) in Bcma-Expressing Cancer Cell Lines", BLOOD, vol. 134, no. 19, 7 November 2019 (2019-11-07), pages 1585-1597, XP055798807, US ISSN: 0006-4971, DOI: 10.1182/blood.2019000050 Retrieved from the Internet: URL:http://ashpublications.org/blood/article-pdf/134/19/1585/1505398/bloodbld2019000050.pdf> the whole document -----	1-61
Y	US 2011/020232 A1 (EBERHART CHARLES [US] ET AL) 27 January 2011 (2011-01-27) paragraph [0265] - paragraph [0270] -----	1-61

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2021/060276

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:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2021/060276

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2020208572 A1	15-10-2020	AU 2020270555 A1 CA 3136285 A1 CN 113924318 A EP 3953387 A1 KR 20210150488 A WO 2020208572 A1	28-10-2021 15-10-2020 11-01-2022 16-02-2022 10-12-2021 15-10-2020
WO 2018201051 A1	01-11-2018	EP 3615068 A1 US 2020179511 A1 WO 2018201051 A1	04-03-2020 11-06-2020 01-11-2018
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