

A DOSING REGIMEN

RELATED APPLICATION DATA

[0001] The present application claims priority from Australian Patent Application No. 2023900983 filed on 4 April 2023 entitled “A Dosing Regimen”. The entire contents of which is hereby incorporated by reference.

SEQUENCE LISTING

[0002] The present application is filed together with a Sequence Listing in electronic form. The entire contents of the Sequence Listing are hereby incorporated by reference.

FIELD OF THE INVENTION

[0003] The present disclosure relates to combination dosing regimen comprising an anti-KMA antibody, an IMiD/CELMoD and a steroid. Such combinations may be used for the treatment of multiple myeloma.

BACKGROUND OF THE INVENTION

[0004] Multiple myeloma represents a malignant proliferation of plasma cells derived from a single clone. The multiple myeloma tumor, its products, and the patient's response to it can result in a number of organ dysfunctions, symptoms of bone pain or fracture, renal failure, susceptibility to infection, anaemia, hypocalcaemia, clotting abnormalities, neurologic symptoms and vascular manifestations of hyperviscosity.

[0005] Despite numerous treatment options, multiple myeloma remains an incurable disease for most patients with no effective long-term treatment that currently exists for multiple myeloma. For example, the current chance of surviving for 5 years post initial diagnosis in Australia and the USA is 55%. Accordingly, new methods of treatment are needed.

SUMMARY OF THE INVENTION

[0006] Monoclonal antibodies are considered to have a high potential for immunotoxicity, which can be dose dependent. Thus, in cases where a low dose of a monoclonal antibody would be considered to be effective for therapeutic treatment, higher doses are often not contemplated.

[0007] Early investigational studies of anti-KMA antibodies suggested that they were not subject to the phenomenon known as “antigen sink”. As such, taken together with the known

potential for monoclonal antibody induced immunotoxicity at higher doses, anti-KMA antibodies were considered good candidates for low dosing.

[0008] However, phase II studies surprisingly demonstrated that administration of an anti-KMA antibody at a dose of 10 mg/kg provided an advantageous safety profile in human subjects. This advantageous safety profile was a result of the anti-KMA antibody unexpectedly not depleting immune cells, either alone or, more particularly in conjunction with an immunomodulatory drug (IMiD) or cereblon E3 ligase modulator (CELMoD) and a steroid. In addition, when kappaMab (KM) was administered in conjunction with an IMiD and a steroid (e.g., lenalidomide / dexamethasone), the safety profile of this combination was comparable to that of lenalidomide / dexamethasone administered in combination in the literature (e.g., there were no increases in rates of thrombocytopenia, neutropenia or infection in the KM / lenalidomide / dexamethasone treated patients compared to lenalidomide / dexamethasone alone).

[0009] The observed safety profile is surprising because, administration of other monoclonal antibodies in the treatment of multiple myeloma typically results in depletion of immune cells due to the antigen target being present on both the malignant plasma cells and on healthy immune cells (e.g., BCMA and CD38). Thus, the present inventor's findings support higher dosing of anti-KMA antibodies (e.g., above 10 mg/kg), such as KM, and particularly in conjunction with an IMiD or a CELMoD and a steroid. This is a significant advance in the art because increased anti-KMA antibody dosing, in particular in conjunction with and an IMiD or a CELMoD and a steroid may improve outcomes in patients with multiple myeloma, in particular those patients whose multiple myeloma has relapsed or is refractory.

[0010] Accordingly, in one example, the present disclosure relates to a method of treating multiple myeloma in a subject in need thereof, the method comprising administering to the subject a treatment which comprises:

- at least 30 mg/kg of an anti-KMA antibody;
- an IMiD or a CELMoD; and
- a steroid.

[0011] The methods of the present disclosure also relate to a combination dosing regimen for use in the treatment of multiple myeloma in a subject comprising:

- at least 30 mg/kg of an anti-KMA antibody;
- an IMiD or a CELMoD; and
- a steroid.

[0012] The methods of the present disclosure further relate to a kit comprising:

a single dose or multiple doses of at least 30 mg/kg of an anti-KMA antibody;
a single dose or multiple doses of an IMiD or a CELMoD;
a single dose or multiple doses of a steroid;
instructions for using the anti-KMA antibody, the IMiD or the CELMoD, and the steroid, for the treatment of multiple myeloma in a subject.

[0013] In the above examples, the anti-KMA antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), the VH comprising a complementarity determining region (CDR) 1 comprising an amino acid sequence as shown in SEQ ID NO: 6, a CDR2 comprising an amino acid sequence as shown in SEQ ID NO: 7 and a CDR3 comprising a sequence as shown in SEQ ID NO: 8 and the VL comprising a CDR 1 comprising an amino acid sequence as shown in SEQ ID NO: 9, a CDR2 comprising an amino acid sequence as shown in SEQ ID NO: 10 and a CDR3 comprising a sequence as shown in SEQ ID NO: 11. In another example, the anti-KMA antibody has a VH comprising a sequence set forth in SEQ ID NO: 1 and a VL comprising a sequence set forth in SEQ ID NO: 2.

[0014] In an example, about 30 mg/kg to about 60 mg/kg of the anti-KMA antibody is administered to the subject. For example, 30 mg/kg to 60 mg/kg of the anti-KMA antibody is administered to the subject. In an example, about 30 mg/kg of the anti-KMA antibody is administered to the subject. For example, 30 mg/kg of the anti-KMA antibody is administered to the subject. In another example, about 45 mg/kg of the anti-KMA antibody is administered to the subject. For example, 45 mg/kg of the anti-KMA antibody is administered to the subject. In a further example, about 60 mg/kg of the anti-KMA antibody is administered to the subject. For example, 60 mg/kg of the anti-KMA antibody is administered to the subject.

[0015] In an example, the IMiD is lenalidomide, pomalidomide or thalidomide. For example, the IMiD can be lenalidomide. In an example, the CELMoD is iberdomide or CC-92480. For example, the CELMoD is iberdomide. In an example, about 25 mg of the IMiD or the CELMoD is administered to the subject. In an example, 25 mg of the IMiD or the CELMoD is administered to the subject. For example, about 25 mg of lenalidomide is administered to the subject. In one example, 25 mg of lenalidomide is administered to the subject.

[0016] In an example, the steroid is dexamethasone or prednisone. For example, the steroid is dexamethasone. In an example, about 40 mg of the steroid is administered to the subject. In an example, 40 mg of the steroid is administered to the subject. For example, about 40 mg of dexamethasone is administered to the subject. In one example, 40 mg of dexamethasone is administered to the subject.

[0017] In an example a method of treating multiple myeloma in a subject in need thereof, the method comprising administering to the subject a treatment which comprises:

- at least 30 mg/kg of an anti-KMA antibody;
- 25 mg of an IMiD or a CELMoD; and
- 40 mg of steroid.

[0018] In an example a method of treating multiple myeloma in a subject in need thereof, the method comprising administering to the subject a treatment which comprises:

- at least 30 mg/kg of an anti-KMA antibody having the CDRs of KM;
- 25 mg of lenalidomide; and
- 40 mg of dexamethasone.

[0019] In an example, treatment comprises administering to the subject in a treatment phase: at least 30 mg/kg of the anti-KMA antibody once per week;

- the IMiD or the CELMoD once per day; and
- the steroid once per week.

[0020] In an example, the duration of the treatment phase is between at least 6 weeks and at least 10 weeks. For example, the duration of the treatment phase is between 6 weeks and 10 weeks. In an example, the duration of the treatment phase is at least 8 weeks. For example, the duration of the treatment phase is 8 weeks.

[0021] In an example, the methods of the present disclosure further comprise administering to the subject the IMiD or the CELMoD once per day for at least 3 weeks prior to the start of the treatment phase. For example, the methods of the present disclosure further comprise administering to the subject the IMiD or the CELMoD once per day for 3 weeks prior to the start of the treatment phase.

[0022] In an example, the methods of the present disclosure further comprise administering a steroid to the subject at least 1 week prior to the start of the treatment phase. For example, the methods of the present disclosure further comprise administering a steroid to the subject 1 week prior to the start of the treatment phase.

[0023] In an example, the subject's immune cells are maintained at levels corresponding with their immune cells prior to administration of the anti-KMA antibody. In another example, the subject's immune cells are maintained at levels corresponding with their immune cells after the treatment phase. In an example, the subject's immune cells are one or more or all of red blood cells; white blood cells; and platelets.

[0024] In an example, treatment comprises administering to the subject in a treatment phase: at least 30 mg/kg of the anti-KMA antibody once per week;

25 mg of the IMiD or the CELMoD once per day; and
40 mg of the steroid once per week.

[0025] In an example, treatment comprises administering to the subject in a treatment phase:
at least 30 mg/kg of an anti-KMA antibody having the CDRs of KM once per week;
25 mg of lenalidomide once per day; and
40 mg of dexamethasone once per week.

[0026] In an example, the methods of the present disclosure further comprise a maintenance phase which comprises administering to the subject:
at least 30 mg/kg of the anti-KMA antibody once per month;
the IMiD or the CELMoD once per day; and
the steroid once per week.

[0027] In an example, the methods of the present disclosure further comprise a maintenance phase which comprises administering to the subject:
at least 30 mg/kg of the anti-KMA antibody once per month;
25 mg of the IMiD or the CELMoD once per day; and
40 mg of the steroid once per week.

[0028] In an example, the methods of the present disclosure further comprise a maintenance phase which comprises administering to the subject:
at least 30 mg/kg of an anti-KMA antibody having the CDRs of KM once per week;
25 mg of lenalidomide once per day; and
40 mg of dexamethasone once per week.

[0029] In an example, the maintenance phase follows after the treatment phase. In an example, the duration of the maintenance phase is at least 12 weeks. For example, the duration of the maintenance phase is 12 weeks. In another example, the maintenance phase continues until disease progression.

[0030] After a subject reaches disease progression, the subject is taken off the therapy. In one example, the subject is put onto another anti-multiple myeloma therapy. In another example, the maintenance phase is stopped.

[0031] In an example, the anti-KMA antibody is formulated for intravenous infusion. In an example, the IMiD or the CELMoD is formulated for oral delivery. In an example, the steroid is formulated for oral delivery or intravenous infusion.

[0032] In an example, the subject has received at least one, at least two, at least three, at least four, at least five or at least six prior lines of therapy.

[0033] In an example, the subject achieved at least a minimal response (e.g., a 25% reduction in M protein) to their most recent line of therapy.

[0034] In an example, the subject is refractory to at least one, at least two, at least three or at least four prior lines of therapy. In an example, the subject is refractory to at least one proteasome inhibitor, IMiD, CELMoD or autologous stem cell transplantation.

[0035] In an example, the subject has relapsed myeloma. In an example, the subject's multiple myeloma has relapsed and is refractory to at least one proteasome inhibitor, IMiD, CELMoD or autologous stem cell transplantation.

[0036] In an example, the subject has no prior exposure to the IMiD or the CELMoD. For example, the subject has no prior exposure to lenalidomide.

[0037] Any example herein shall be taken to apply *mutatis mutandis* to any other example unless specifically stated otherwise.

[0038] The present invention is not to be limited in scope by the specific examples described herein, which are intended for the purpose of exemplification only. Functionally-equivalent products, compositions and methods are clearly within the scope of the invention, as described herein.

[0039] Throughout this specification, unless specifically stated otherwise or the context requires otherwise, reference to a single step, composition of matter, group of steps or group of compositions of matter shall be taken to encompass one and a plurality (i.e. one or more) of those steps, compositions of matter, groups of steps or group of compositions of matter.

[0040] The invention is hereinafter described by way of the following non-limiting Examples and with reference to the accompanying drawings.

KEY TO SEQUENCE LISTING

SEQ ID NO: 1 – amino acid sequence of KappaMab variable heavy chain (VH)

SEQ ID NO: 2 – amino acid sequence of KappaMab variable light chain (VL)

SEQ ID NO: 3 – amino acid sequence of KMA switch region in kappa light chain

SEQ ID NO: 4 – amino acid sequence of KappaMab epitope

SEQ ID NO: 5 – amino acid sequence of KappaMab epitope 2 (improved binding)

SEQ ID NO: 6 – amino acid sequence of KappaMab VH CDR1

SEQ ID NO: 7 – amino acid sequence of KappaMab VH CDR2

SEQ ID NO: 8 – amino acid sequence of KappaMab VH CDR3

SEQ ID NO: 9 – amino acid sequence of KappaMab VL CDR1

SEQ ID NO: 10 – amino acid sequence of KappaMab VL CDR2

SEQ ID NO: 11 – amino acid sequence of KappaMab VL CDR3

SEQ ID NO: 12 – amino acid sequence of K121 VH

SEQ ID NO: 13 – amino acid sequence of K121 VC

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

[0041] **Figure 1. Study schema.** Stage 1 involved 8 weekly doses of 10 mg/kg KappaMab, followed by monthly dosing until progression. Stage 2 was 8 weekly doses of 10 mg/kg KappaMab plus 25 mg lenalidomide and 40 mg dexamethasone, followed by monthly dosing of KappaMab plus lenalidomide and dexamethasone until progression. In Stage 2, Cycle 1 was 35 days, with a one-week administration of LEN and DEX prior to the first dose of KappaMab. The remaining cycles were 28 days, with KappaMab administration on Day 1 of each Cycle.

[0042] **Figure 2. Duration of response in Stage KM-Rd treated patients.** Shaded region indicates the 95% confidence interval for the probability of remaining in response at each time point.

[0043] **Figure 3. Cumulative incidences for the occurrence of the next treatment or the competing event of death before next treatment.** Shaded regions indicate the 95% confidence intervals for each type of event at each time point.

[0044] **Figure 4. ORR and best clinical response rate comparisons between Stage 2 KM-Rd and the Rd-MRDR patients.** A comparison of the best clinical responses for the Rd-MRDR group with patients in Stage 2 showed that Stage 2 patients overall had higher percentages of best clinical responses with more responses and improved quality of response. In addition, Stage 2 (KM-Rd patients) had an ORR of 83% and a CBR of 93% compared to an ORR of 45% in matched controls from the Australian and New Zealand Myeloma and Related Diseases registry (Rd-MRDR group).

[0045] **Figure 5. Comparisons of the time-to-event overall survival endpoint comparing the KM-Rd group with Rd-MRDR group.** The logrank test showed a significance of $p=0.0163$, and the hazard ratio with 95% confidence interval was HR 0.46, 95% CI (0.2466, 0.8679). Median OS in the Rd-MRDR group was 27.8 months, and median OS was not reached in the KM-Rd group. For mortality data, in the KM-Rd cohort ($n=40$), 9 patients had evaluable data and 31 patients were censored, while in the Rd-MRDR group ($n=77$), 32 patients had evaluable data and 45 patients were censored.

[0046] **Figure 6. Serial M protein and FLC levels for Stage 1 (Panels A and B) and Stage 2 (Panels C and D).** In Stage 1, M protein levels decreased below baseline for 1 patient (Panel A, open upside down triangles), but FLC increased for this patient (Panel B). In Stage

1, one FLC-only MM patient showed decreased sFLC levels ranging between -36% and -80% from baseline for 31 cycles of treatment (**Panel B, open dotted circles**). In Stage 2, the majority of patients responded to KM-Rd (**Panel C**). Median % change from baseline for FLC was elevated to Cycle 3 (i.e., after 9 doses of KM), then it reduced and remained below baseline (**Panel D red line**). This was not observed in the Stage 1 patients, where median FLC fell between Cycles 3 and 4, then generally elevated followed Cycle 4 (**Panel B red line**). Median is a white line that is marked by an arrow in the Figure.

DETAILED DESCRIPTION OF THE INVENTION

General Techniques and Selected Definitions

[0047] Unless specifically defined otherwise, all technical and scientific terms used herein shall be taken to have the same meaning as commonly understood by one of ordinary skill in the art (e.g., molecular biology, biochemistry, oncology and clinical studies).

[0048] Unless otherwise indicated, the molecular and statistical techniques utilized in the present disclosure are standard procedures, well known to those skilled in the art. Such techniques are described and explained throughout the literature in sources such as, J. Perbal, A Practical Guide to Molecular Cloning, John Wiley and Sons (1984), J. Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbour Laboratory Press (1989), T.A. Brown (editor), Essential Molecular Biology: A Practical Approach, Volumes 1 and 2, IRL Press (1991), D.M. Glover and B.D. Hames (editors), DNA Cloning: A Practical Approach, Volumes 1-4, IRL Press (1995 and 1996), and F.M. Ausubel et al. (editors), Current Protocols in Molecular Biology, Greene Pub. Associates and Wiley-Interscience (1988, including all updates until present), Ed Harlow and David Lane (editors) Antibodies: A Laboratory Manual, Cold Spring Harbour Laboratory, (1988), and J.E. Coligan et al. (editors) Current Protocols in Immunology, John Wiley & Sons (including all updates until present).

[0049] One of skill in the art will be aware that an “antibody” is generally considered to be a protein that comprises a variable region made up of a plurality of polypeptide chains, e.g., a polypeptide comprising a V_L and a polypeptide comprising a V_H . An antibody also generally comprises constant domains, some of which can be arranged into a constant region or constant fragment or fragment crystallizable (Fc). A V_H and a V_L interact to form a Fv comprising an antigen binding region that specifically binds to one or a few closely related antigens. Generally, a light chain from mammals is either a κ light chain or a λ light chain and a heavy chain from mammals is α , δ , ϵ , γ , or μ . Antibodies can be of any type (e.g., IgG, IgE, IgM, IgD, IgA, and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass. The term

“antibody” also encompasses humanized antibodies, primatized antibodies, human antibodies and chimeric antibodies.

[0050] The terms “full-length antibody”, “intact antibody” or “whole antibody” are used interchangeably to refer to an antibody in its substantially intact form, as opposed to an antigen binding fragment of an antibody. Specifically, whole antibodies include those with heavy and light chains including an Fc region. The constant domains may be wild-type sequence constant domains (e.g., human wild-type sequence constant domains) or amino acid sequence variants thereof.

[0051] An “antigen binding fragment” of an antibody comprises one or more variable regions of an intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂ and Fv fragments (scFv, di-scFv, tri-scFv); diabodies; linear antibodies; single-chain antibody molecules and multispecific antibodies formed from antibody fragments.

[0052] The term “complementarity determining regions” (syn. CDRs; i.e., CDR1, CDR2, and CDR3) is used in the context of the present disclosure to refer to the amino acid residues of an antibody variable region the presence of which are major contributors to specific antigen binding. Each variable region typically has three CDR regions identified as CDR1, CDR2 and CDR3. In one example, the amino acid positions assigned to CDRs and FRs are defined according to Kabat Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., 1987 and 1991 (also referred to herein as “the Kabat numbering system”).

[0053] As used herein, “variable region” refers to the portions of the light and/or heavy chains of an antibody as defined herein that specifically binds to an antigen and, for example, includes amino acid sequences of CDRs; i.e., CDR1, CDR2, and CDR3, and framework regions (FRs). For example, the variable region comprises three or four FRs (e.g., FR1, FR2, FR3 and optionally FR4) together with three CDRs. V_H refers to the variable region of the heavy chain. V_L refers to the variable region of the light chain.

[0054] In one example, the amino acid positions assigned to CDRs and FRs are defined according to Kabat Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., 1987 and 1991 (also referred to herein as “the Kabat numbering system” or “Kabat”).

[0055] Other conventions that include corrections or alternate numbering systems for variable domains include IMGT (Lefranc, et al. (2003), Dev Comp Immunol 27: 55- 77), Chothia (Chothia C, Lesk AM (1987), J Mol Biol 196: 901-917; Chothia, et al. (1989), Nature 342: 877-883) and AHo (Honegger A, Plückthun A (2001) J Mol Biol 309: 657-670). For

convenience, examples of binding proteins of the present disclosure may also be labelled according to IMGT.

[0056] The term “antibody heavy chain” is used herein to refer to the larger of the two types of polypeptide chains present in all antibody molecules in their naturally occurring conformations. An “antibody light chain,” as used herein, refers to the smaller of the two types of polypeptide chains present in all antibody molecules in their naturally occurring conformations. κ and λ light chains refer to the two major antibody light chain isotypes.

[0057] As used herein, the term “binds” in reference to the interaction of an antibody or antigen binding fragment thereof with an antigen means that the interaction is dependent upon the presence of a particular structure (e.g., an antigenic determinant or epitope) on the antigen. For example, an antibody recognizes and binds to a specific protein structure rather than to proteins generally. If an antibody binds to epitope “A”, the presence of a molecule containing epitope “A” (or free, unlabelled “A”), in a reaction containing labelled “A” and the antibody, will reduce the amount of labelled “A” bound to the antibody.

[0058] As used herein, the term “specifically binds” shall be taken to mean that the binding interaction between an antibody or antigen binding fragment thereof and kappa myeloma antigen is dependent on the presence of the antigenic determinant or epitope of kappa myeloma antigen bound by the antibody or antigen binding fragment thereof. Accordingly, the antibody or antigen binding fragment thereof preferentially binds or recognizes a kappa myeloma antigen determinant or epitope even when present in a mixture of other molecules or organisms. In one example, the antibody or antigen binding fragment thereof reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with kappa myeloma antigen or a cell expressing the same than it does with alternative antigens or cells. It is also understood by reading this definition that, for example, an antibody or antigen binding fragment thereof that specifically binds to kappa myeloma antigen may or may not specifically bind to a second antigen. As such, “specific binding” does not necessarily require exclusive binding or non-detectable binding of another antigen. The term “specifically binds” can be used interchangeably with “selectively binds” herein. Generally, reference herein to binding means specific binding, and each term shall be understood to provide explicit support for the other term.

[0059] Methods for determining specific binding will be apparent to the skilled person. In an example, an anti-KMA antibody according to the present disclosure is contacted with kappa myeloma antigen or a cell expressing same or a mutant form thereof or an alternative antigen. The binding of the antibody to the kappa myeloma antigen or mutant form or alternative antigen

is then determined and an antibody that binds as set out above to the kappa myeloma antigen rather than the mutant or alternative antigen is considered to specifically bind to kappa myeloma antigen.

[0060] The term “antigen sink” is used in the context of the present disclosure to describe a monoclonal antibody that binds to an unintended target (e.g., healthy cells) that prevents the antibodies from reaching the intended tumor antigen targets *in vivo* as these unintended targets will “sop up” the antibody, serving as a sink

[0061] The phrase “a combination dosing regimen” is used in the context of the present disclosure to refer to a combination of therapeutics that are administered to a subject according to a dosing regimen disclosed herein.

[0062] As used herein, the term “subject” or “patient” may be used interchangeably and shall be taken to mean any animal including humans, for example, a mammal. Exemplary subjects include but are not limited to humans and non-human primates. For example, the subject is a human.

[0063] The phrase “therapeutic” is used in the context of the present disclosure to refer to a treatment, therapy, or drug.

[0064] One of skill in the art would appreciate that the therapeutics disclosed herein are generally administered in phases. For example, a “treatment phase” refers to a period of time that is used to gain rapid control the multiple myeloma and relieve symptoms. In certain examples, there is an induction phase prior to the treatment phase.

[0065] The phrase “induction phase” as used herein is used to refer to a period of time before the treatment phase starts.

[0066] In certain examples, the treatment phase is followed by a maintenance phase. The phrase “maintenance phase” as used herein is used to refer to a period of time in which treatment of the therapeutic is continued in order to inhibit or, in certain examples, prevent recurrence of the multiple myeloma.

[0067] As used herein, the terms “once per day” or “daily” in the context of dosing refers to a total dose of a drug (e.g. lenalidomide) administered to a subject in a day. The dose may be divided to two or more administrations during the day, or given as one administration per day. For example, the total dose may be 25 mg administered daily as a single dose.

[0068] As used herein, the terms “once per week”, “weekly” or “at least one week” in the context of dosing refers to an approximate number, and can include every seven days $\pm$ two days, i.e., every five days to every nine days. The dosing frequency of “once per week” can be every five days, every six days, every seven days, every eight days, or every nine days.

[0069] As used herein, the terms “once per month”, “monthly” or “at least four weeks” in the context of dosing refers to an approximate number, and can include every 28 days $\pm$ 1 week, i.e., every 21 to every 35 days. The dosing frequency of “once per month” can be every 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, every 27 days, every 28 days, every 29 days, every 30 days, every 31 days, every 32 days, every 33 days, every 34 days or every 35 days.

[0070] The terms “carrier” and “excipient” refer to compositions of matter that are conventionally used in the art to facilitate the storage, administration, and/or the biological activity of an active compound (see, e.g., Remington's Pharmaceutical Sciences, 16th Ed., Mac Publishing Company (1980). A carrier may also reduce any undesirable side effects of the active compound. A suitable carrier is, for example, stable, e.g., incapable of reacting with other ingredients in the carrier. In one example, the carrier does not produce significant local or systemic adverse effect in recipients at the dosages and concentrations employed for treatment.

[0071] Suitable carriers for the present disclosure include those conventionally used, e.g., water, saline, aqueous dextrose, lactose, Ringer's solution, a buffered solution, hyaluronan and glycols are exemplary liquid carriers, particularly (when isotonic) for solutions. Suitable pharmaceutical carriers and excipients include starch, cellulose, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, glycerol, propylene glycol, water, ethanol, and the like.

[0072] The term “analyte” is used in the context of the present disclosure to refer to a molecule whose presence in a sample provides a quantitative or qualitative measure of gene expression. Exemplary analytes informative of gene expression levels include RNA and protein. Various methods of determining RNA and protein levels are known in the art. Exemplary methods include whole genome sequencing, next generation sequencing, NanoString technology, droplet digital PCR, quantitative RT-PCR, mass spectrometry, immunohistochemistry and multiplex immunoassay. In an example, the analyte is a cytokine which is measured using a multiplex immunoassay (e.g. Bio-Plex Pro Human Cytokine assay; Bio-Rad).

[0073] As used in this specification and the appended claims, terms in the singular and the singular forms “a,” “an” and “the,” for example, optionally include plural referents unless the content clearly dictates otherwise.

[0074] As used herein, the term “about”, unless stated to the contrary, refers to $\pm$ 10%, more preferably $\pm$ 5%, more preferably $\pm$ 1%, of the designated value.

[0075] The term “and/or”, e.g., “X and/or Y” shall be understood to mean either “X and Y” or “X or Y” and shall be taken to provide explicit support for both meanings or for either meaning.

[0076] Throughout this specification the word “comprise”, or variations such as “comprises” or “comprising”, will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

Combination Dosing Regimen

Therapeutics

[0077] The phrase “anti-KMA antibody” is used in the context of the present disclosure to refer to an antibody that binds or specifically binds Kappa Myeloma Antigen (KMA). KMA is a membrane-bound light chain with selectivity for kappa myeloma cells (Boux, HA. et al. (1983) J Exp Med. 158:1769). KMA is a unique cell-surface antigen expressed on malignant plasma cells in kappa restricted multiple myeloma (κ MM), some lymphomas, occasional tonsillar B cells and in-vitro activated B cells, but not on normal B cells in bone marrow.

[0078] In an example, an anti-KMA antibody is capable of binding KMA bearing cells. In another example, an anti-KMA antibody is capable of killing KMA bearing cells. For example, anti-KMA antibodies according to the present disclosure can bind and kill KMA bearing malignant plasma cells. In an example, anti-KMA antibodies according to the present disclosure do not bind intact immunoglobulin. Put another way, exemplary anti-KMA antibodies do not recognise kappa light chains that are in association with Ig heavy chain such as in an intact Ig molecules.

[0079] In an example, anti-KMA antibodies of the disclosure do not bind kappa light chain associated with heavy chain. For example, anti-KMA antibodies do not bind the kappa light chain of an antibody which also comprises a heavy chain.

[0080] For example, the anti-KMA antibody can be the “K121 antibody” disclosed in (Hutchinson et al. 2011) or a variant, antigen binding fragment or humanised form thereof. An exemplary humanized form is referred to in the context of the present disclosure as “kappaMab” or “KM” used interchangeably, an antibody having a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 1 and a light chain variable region (VL) comprising the amino acid sequence set forth in SEQ ID NO: 2. Thus, in an example, the anti-KMA antibody is KM.

[0081] In another example, the anti-KMA antibody binds to or specifically binds to an epitope of KMA that is specifically bound by KM or that competes with KM for binding to KMA, wherein KM has a VH comprising the amino acid sequence set forth in SEQ ID NO: 1 and a VL comprising the amino acid sequence set forth in SEQ ID NO: 2.

[0082] KM binds an epitope of KMA located in the switch region of kappa light chain (SEQ ID NO: 3). Amino acid substitution in the epitope can increase binding affinity of KM (Hutchinson et al. 2011). Accordingly, in an example, an anti-KMA antibody according to the present disclosure competes with an antibody that binds or specifically binds a region comprising an amino acid sequence as shown in SEQ ID NO: 3 with at least one, at least two or at least three amino acid substitutions.

[0083] In another example, an anti-KMA antibody according to the present disclosure competes with an antibody that binds or specifically binds an epitope comprising an amino acid sequence as shown in SEQ ID NO: 4 with at least one, at least two or at least three amino acid substitutions. Exemplary substitutions include conservative amino acid substitutions such as those described below in Table 1. In an example, aspartic acid (Asp (D)) in SEQ ID NO: 4 is substituted with glutamic acid (Glu (E)) (SEQ ID NO: 5). Accordingly, in an example, an anti-KMA antibody according to the present disclosure competes with an antibody that binds or specifically binds an epitope comprising an amino acid sequence as shown in SEQ ID NO: 5.

Table 1. Exemplary substitutions.

Original Residue	Exemplary Substitutions
Arg (R)	Lys (K)
Glu (E)	Asp (D)
Ile (I)	Leu (L); Val (V); Ala (A)
Leu (L)	Ile (I); Val (V); Met (M); Ala (A); Phe (F)
Lys (K)	Arg (R)

[0084] In another example, an anti-KMA antibody according to the present disclosure competes with an antibody that binds or specifically binds an epitope comprising an amino acid sequence as shown in SEQ ID NO: 4. In another example, an anti-KMA antibody according to the present disclosure competes with an antibody that binds or specifically binds an epitope consisting of the amino acid sequence as shown in SEQ ID NO: 4.

[0085] Antibodies may be identified by their ability to compete for binding to KMA or a region or epitope thereof using various methods known in the art. For example, antibody

binding to KMA on kappa human myeloma cell lines (κ HMCL) such as KMS-11, KMS-26 and JJN3 can be assessed (Asvadi et al. 2015). In this procedure, an anti-KMA antibody such as KM is conjugated with biotin using established procedures (Hofmann K, et al. (1982) Biochemistry 21 : 978-84). Antibodies are then evaluated by their capacity to compete with the binding of the biotinylated KM antibody to KMA on κ HMCL cells. The binding of biotinylated KM to κ HMCL cells may be assessed by the addition of fluorescein-labelled streptavidin which will bind to biotin on the labelled antibody. Fluorescence staining of cells is then quantified by flow cytometry, and the competitive effect of antibodies expressed as a percentage of the fluorescence levels obtained in the absence of the competitor.

[0086] In another example, the anti-KMA antibody has a VH comprising the CDRs as shown in SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8 and a VL. In another example, the anti-KMA antibody has a VH and a VL comprising CDRs as shown in SEQ ID NO: 9, SEQ ID NO: 10 and SEQ ID NO: 11. In another example, the anti-KMA antibody has a VH comprising CDRs as shown in SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8 and a VL comprising CDRs as shown in SEQ ID NO: 9, SEQ ID NO: 10 and SEQ ID NO: 11.

[0087] In another example, the anti-KMA antibody has a VH comprising CDRs as shown in SEQ ID NO: 6, SEQ ID NO: 7 SEQ ID NO: 8 and an amino acid sequence at least 90 %, at least 95%, at least 98% or at least 99% identical to SEQ ID NO: 1. In another example, the anti-KMA antibody has a VL comprising CDRs as shown in SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11 and an amino acid sequence at least 90 %, at least 95%, at least 98% or at least 99% identical to SEQ ID NO: 2. In another example, the anti-KMA antibody has a VH comprising CDRs as shown in SEQ ID NO: 6, SEQ ID NO: 7 SEQ ID NO: 8, an amino acid sequence at least 90 %, at least 95%, at least 98% or at least 99% identical to SEQ ID NO: 1 and a VL comprising CDRs as shown in SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11 and an amino acid sequence at least 90 %, at least 95%, at least 98% or at least 99% identical to SEQ ID NO: 2.

[0088] In another example, the anti-KMA antibody has a VH comprising the amino acid sequence shown in SEQ ID NO: 1 and a VL comprising the amino acid sequence shown in SEQ ID NO: 2.

[0089] In another example, the anti-KMA antibody has the CDRs shown in SEQ ID NO: 1 and SEQ ID NO: 2, wherein the CDRs are assigned using the Kabat numbering system. In another example, the anti-KMA antibody has the CDRs shown in SEQ ID NO: 1 and SEQ ID NO: 2, wherein the CDRs are assigned using the IMGT numbering system. In another example,

the anti-KMA antibody has the CDRs shown in SEQ ID NO: 1 and SEQ ID NO: 2, wherein the CDRs are assigned using EU numbering system of Kabat.

[0090] In an example, the anti-KMA antibody is a naked antibody. In other examples, the anti-KMA antibody is a full-length antibody, intact antibody or whole antibody. In an example, the anti-KMA antibody is monospecific.

[0091] In another example, the anti-KMA antibody is an antigen binding fragment comprising CDRs as shown in SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10 and SEQ ID NO: 11.

[0092] In another example, the anti-KMA antibody has a VH comprising the amino acid sequence shown in SEQ ID NO: 12 or a humanised variant thereof and a VL comprising the amino acid sequence shown in SEQ ID NO: 13 or a humanised variant thereof.

[0093] In another example, the anti-KMA antibody has the CDRs shown in SEQ ID NO: 12 and SEQ ID NO: 13 or humanised variants thereof, wherein the CDRs are assigned using the Kabat numbering system. In another example, the anti-KMA antibody has the CDRs shown in SEQ ID NO: 12 and SEQ ID NO: 13 or humanised variants thereof, wherein the CDRs are assigned using the IMGT numbering system. In another example, the anti-KMA antibody has the CDRs shown in SEQ ID NO: 12 and SEQ ID NO: 13 or humanised variants thereof, wherein the CDRs are assigned using EU numbering system of Kabat.

[0094] The term “immunomodulatory drug” or “IMiD” is used in the context of the present disclosure to refer to molecules that have pleiotropic effects including inducing direct apoptosis against malignant tumor cells, interfering with the interaction of the tumor with bone marrow stromal cells, and increasing the anti-tumor immune response.

[0095] In one example, the IMiD is selected from the group consisting of lenalidomide, pomalidomide, and thalidomide.

[0096] For example, the IMiD can be lenalidomide. In one example, the IMiD can be pomalidomide. In another example, the IMiD can be thalidomide.

[0097] The term “CRBN E3 ligase modulator” or “CELMoD” is used in the context of the present disclosure to refer to IMiD derivatives. In one example, the CELMoD is selected from the group consisting of CC-122, CC-220 (iberdomide), CC-90009, CC-92480, MDEG-541 and CC-886. This list is non-limiting and various other IMiDs and CELMoDs are known in the art (e.g. see review by Holstein et al. 2018 incorporated herein by reference).

[0098] For example, the CELMoD can be CC-122. In one example, the CELMoD can be CC-220 (iberdomide). In another example, the CELMoD can be CC-90009. In another

example, the CELMoD can be CC-92480. In another example, the CELMoD can be MDEG-541. In another example, the CELMoD can be CC-886.

[0099] The term “steroid” or “corticosteroid” is used in the context of the present disclosure to refer to a class of steroid hormones that are produced in the adrenal cortex or produced synthetically, such as dexamethasone and prednisone (also referred herein as prednisolone). For example, the steroid can be dexamethasone. In another example, the steroid can be prednisone.

Dosing Regimen

[0100] The present inventors have surprisingly shown that administering an anti-KMA antibody such as KappaMab, and particularly, in combination with lenalidomide and dexamethasone is unexpectedly well tolerated with a favourable safety profile, suggesting that the dose of anti-KMA antibody can be safely increased (e.g. to at least 30 mg/kg and above). Such combinations used in a dosing regimen may be particularly advantageous in view of one or more or all of increased therapeutic potency; improved outcomes; favourable safety profile.

[0101] In an example, a favourable safety profile is determined based on the number or severity of adverse events reported using Common Terminology Criteria for Adverse Events v3.0 (CTCAE). For example, an adverse event may be any unfavourable and unintended event, symptom, or disease temporally associated with the combination dosing regimen.

[0102] In an example, the adverse event may be haematologic or non-haematologic. In an example, the haematologic adverse event may be anaemia, thrombocytopenia, lymphopenia, neutropenia, febrile neutropenia or leukopenia. In an example, the non-haematologic adverse event may be a rash, hyperglycaemia, fatigue, abdominal pain, constipation, diarrhoea, nausea, hypophosphatemia, infusion related reaction, peripheral neuropathy, insomnia, cramps, pain, URTI, pneumonia and cellulitis. In an example, the adverse events may be graded according to severity on a scale of one to four.

[0103] In an example, a favourable safety profile is determined based on assessment of a subject's immune cells after treatment according to the disclosure. In an example, the subject's immune cells are assessed using blood analysis tests, such as, complete blood count (CBC). CBC measures a blood sample from the subject for immune cell parameters such as red blood cells (e.g. haemoglobin and haematocrit), white blood cells (e.g. neutrophils) and platelets.

[0104] For example, the subject is assessed after administration of four to eight doses of an anti-KMA antibody of the disclosure. In an example, the subject is assessed prior to the treatment phase (i.e. prior to administration of the anti-KMA antibody). In an example, the

subject can be assessed after four to eight weeks of the treatment phase. In another example, the subject's immune cells are compared with the subject's immune cells at baseline (i.e. prior to administration of the anti-KMA antibody). In an example, the subject's immune cells are monitored over time and a favourable safety profile is characterised by no significant change of the monitored cell(s). For example, the subject's immune cells can be monitored over time and, a favourable safety profile is characterised by no significant change in the subject's immune cells. In an example, a favourable safety profile is characterised by no change in the subject's immune cells after administration of four doses of an anti-KMA antibody such as KM. In an example, a favourable safety profile is characterised by no change in the subject's immune cells after administration of eight doses of an anti-KMA antibody such as KM. In an example, the immune cells are one or more or all of red blood cells (e.g. haemoglobin and haematocrit); white blood cells (e.g. neutrophils); and platelets.

[0105] In an example, anaemia can be diagnosed using haemoglobin as a parameter. For example, mild anaemia can be diagnosed under the National Cancer Institute (NCI) criteria as haemoglobin levels of 10 g/dL to a lower limit of normal. In an example, moderate anaemia can be diagnosed under the NCI criteria as haemoglobin levels between 10 – 8 g/dL. In an example, severe anaemia can be diagnosed under the NCI criteria as haemoglobin levels between 7.9 – 6.5 g/dL. In an example, life-threatening anaemia can be diagnosed under the NCI criteria as haemoglobin levels lower than 6.5 g/dL.

[0106] For example, grade one anaemia can be diagnosed under CTCAE grading as haemoglobin levels < institutional lower limit of normal (LLN) - 10 g/dL; < LLN - 6.2 mmol/L; < LLN - 100 g/L around 10 g/dL. In an example, grade two anaemia can be diagnosed under CTCAE grading as haemoglobin levels < 10.0 - 8.0 g/dL; < 6.2 - 4.9 mmol/L; < 100 - 80 g/L. In an example, grade three anaemia can be diagnosed under CTCAE grading as haemoglobin levels < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L.

[0107] In an example, thrombocytopenia can be diagnosed using platelet count as a parameter. For example, grade one thrombocytopenia can be diagnosed as a platelet count of 75 to < 100 × 10⁹/L. In an example, grade two thrombocytopenia can be diagnosed as a platelet count of 50 to < 75 × 10⁹/L. In an example, grade three thrombocytopenia can be diagnosed as a platelet count of 25 to < 50 × 10⁹/L. In an example, grade four thrombocytopenia can be diagnosed as a platelet count of < 25 × 10⁹/L. It will be understood that platelet thresholds are based on those clinically relevant for chemotherapy and grades 2 to 4 CTCAE V5.0.

[0108] In an example, neutropenia can be diagnosed using absolute neutrophil count as a parameter. For example, grade one neutropenia can be diagnosed as an absolute neutrophil

count (ANC) around 1,500 ANC/ μ L. In an example, grade two neutropenia can be diagnosed as an absolute neutrophil count between 1,500 – 1,000 ANC/ μ L. In an example, grade three neutropenia can be diagnosed as an absolute neutrophil count between 1,000 – 500 ANC/ μ L. In an example, grade four neutropenia can be diagnosed as an absolute neutrophil count lower than 500 ANC/ μ L.

[0109] In an example, the dose of an anti-KMA antibody disclosed herein is at least 30 mg/kg. In another example, the dose of the anti-KMA antibody ranges from about 30 mg/kg to about 90 mg/kg. In one example, the dose of the anti-KMA antibody ranges from 30 mg/kg to 90 mg/kg. In another example, the dose of the anti-KMA antibody ranges from about 30 mg/kg to about 60 mg/kg. In one example, the dose of the anti-KMA antibody ranges from 30 mg/kg to 60 mg/kg. In another example, the dose of the anti-KMA antibody ranges from about 30 mg/kg to about 45 mg/kg. In one example, the dose of the anti-KMA antibody ranges from 30 mg/kg to 45 mg/kg. In another example, the dose of the anti-KMA antibody is 30 mg/kg. In another example, the dose of the anti-KMA antibody is 45 mg/kg. In another example, the dose of the anti-KMA antibody is 60 mg/kg. In another example, the dose of the anti-KMA antibody is 90 mg/kg.

[0110] As will be appreciated by those of skill in the art, the appropriate dose of the IMiD or the CELMoD will depend on the IMiD or the CELMoD being administered. Exemplary general doses of the IMiD or the CELMoD range from about 5 mg to about 300 mg. For example, the dose of the IMiD or the CELMoD range from 5 mg to 300 mg. In one example, the dose of the IMiD or the CELMoD ranges from about 10 mg to about 200 mg. For example, the dose of the IMiD or the CELMoD ranges from 10 mg to 200 mg. In an example, the dose of the IMiD or the CELMoD ranges from about 10 mg to about 25 mg. For example, the dose of the IMiD or the CELMoD ranges from 10 mg to 25 mg. In another example, the dose of the IMiD or the CELMoD is about 10 mg. In one example, the dose of the IMiD or the CELMoD is 10 mg. In another example, the dose of the IMiD or the CELMoD is about 15 mg. In one example, the dose of the IMiD or the CELMoD is 15 mg. In another example, the dose of the IMiD or the CELMoD is about 25 mg. In one example, the dose of the IMiD or the CELMoD is 25 mg.

[0111] In an example, the dose of lenalidomide ranges from about 5 mg to about 300 mg. For example, the dose of lenalidomide ranges from 5 mg to 300 mg. In one example, the dose of lenalidomide ranges from about 10 mg to about 200 mg. For example, the dose of lenalidomide ranges from 10 mg to 200 mg. In an example, the dose of lenalidomide ranges from about 10 mg to about 25 mg. For example, the dose of lenalidomide ranges from 10 mg

to 25 mg. In another example, the dose of lenalidomide is about 10 mg. In one example, the dose of lenalidomide is 10 mg. In another example, the dose of lenalidomide is about 15 mg. In one example, the dose of lenalidomide is 15 mg. In another example, the dose of lenalidomide is about 25 mg. In one example, the dose of lenalidomide is 25 mg.

[0112] Appropriate ImiD or CELMoD dosing can also be obtained from prescribing information. For example, lenalidomide can be administered at 25 mg for newly diagnosed subjects. In one example, lenalidomide can be initially administered at 10 mg before being increased to 15 mg or 25 mg if well tolerated.

[0113] The appropriate dose of the steroid will depend on the steroid being administered. Exemplary general doses of a steroid range from about 5 mg to about 300 mg. For example, the dose of the steroid ranges from 5 mg to 300 mg. In one example, the dose of the steroid ranges from about 10 mg to about 100 mg. In one example, the dose of the steroid ranges from 10 mg to 100 mg. In an example, the dose of the steroid ranges from about 40 mg to about 60 mg. In an example, the dose of the steroid ranges from 40 mg to 60 mg. In another example, the dose of the steroid is about 40 mg. In one example, the dose of the steroid is 40 mg. In another example, the dose of the steroid is about 60 mg. In one example, the dose of the steroid is 60 mg. In another example, the dose of the steroid is about 25 mg. In one example, the dose of the steroid is 25 mg.

[0114] In an example, the dose of dexamethasone ranges from about 5 mg to about 300 mg. In an example, the dose of dexamethasone ranges from 5 mg to 300 mg. In one example, the dose of dexamethasone ranges from about 10 mg to about 100 mg. In one example, the dose of dexamethasone ranges from 10 mg to 100 mg. In an example, the dose of dexamethasone ranges from about 40 mg to about 60 mg. In an example, the dose of dexamethasone ranges from 40 mg to 60 mg. In another example, the dose of dexamethasone is about 40 mg. In one example, the dose of dexamethasone is 40 mg. In another example, the dose of dexamethasone is about 60 mg. In one example, the dose of dexamethasone is 60 mg. In another example, the dose of dexamethasone is about 25 mg. In one example, the dose of dexamethasone is 25 mg.

[0115] Appropriate steroid dosing can also be obtained from prescribing information and, if required, amended based on clinical response. For example, dexamethasone can be administered at 40 mg and reduced if there are specific side effects.

Treatment Phase

[0116] Treatment phase according to the present disclosure comprises administering an anti-KMA antibody, such as KM, an ImiD or a CELMoD and, a steroid. In an example, the

treatment phase may comprise administration of an anti-KMA antibody about once per week, an ImiD or a CELMoD about once per day, and a steroid about once per week. In an example, the treatment phase comprises administration of the anti-KMA antibody once per week (i.e. once weekly). In an example, the treatment phase comprises administration of the anti-KMA antibody weekly for at least four, at least five, at least six, at least seven, at least eight, at least nine or at least 10 weeks. In an example, the treatment phase comprises administration of the anti-KMA antibody weekly for about eight weeks. In these examples, weekly administration can be referred to as a treatment dose (i.e., treatment phase). The dose of the anti-KMA antibody may be increased or decreased throughout the treatment phase as required. For example, the treatment phase may comprise administration of KM once per week.

[0117] In one example, the dose of the anti-KMA antibody may be stopped for a period of time as required (e.g., when trying to resolve a severe adverse event, or as a result of subject non-compliance). In another example, the dose of the anti-KMA antibody may be delayed for a period of time as required. In another example, the dose of the anti-KMA antibody may be reduced for a period of time as required.

[0118] In an example, the treatment phase may comprise administration of the IMiD or the CELMoD once per day (i.e. once daily). In another example, the treatment phase may comprise administration of the IMiD or the CELMoD once every second day. In another example, the treatment phase may comprise administration of the IMiD or the CELMoD once every third day. The dose of the IMiD or the CELMoD may be increased or decreased throughout the treatment phase as required. For example, the treatment phase may comprise administration of lenalidomide once per day.

[0119] In an example, the treatment phase may comprise administration of the steroid once per week (i.e. weekly). In another example, the treatment phase may comprise administration of the steroid once every second week (i.e. fortnightly). In another example, the treatment phase may comprise administration of the steroid once every third week. In another example, the treatment phase may comprise administration of the steroid once every fourth week. The dose of the steroid may be increased or decreased throughout the treatment phase as required. For example, the treatment phase may comprise administration of dexamethasone once per week.

[0120] In an example, the duration of the treatment phase is at least four, at least five, at least six, at least seven, at least eight, at least nine, at least 10, at least 11 or at least 12 weeks. In an example, the duration of the treatment phase is at least six weeks to at least 10 weeks. In another example, the duration of the treatment phase is at least eight weeks.

Induction Phase

[0121] In certain examples, methods of the present disclosure comprise an induction phase. In an example, the induction phase precedes a treatment phase. In an example, an induction phase precedes administration of an anti-KMA antibody to the subject. In an example, the induction phase comprises administration of the IMiD or the CELMoD with the intention of reducing multiple myeloma cell proliferation and improving the response to an anti-KMA antibody. In an example, the induction phase may comprise administration of the IMiD or the CELMoD once per day (i.e. once daily). In another example, the induction phase may comprise administration of the IMiD or the CELMoD once every second day. In another example, the induction phase may comprise administration of the IMiD or the CELMoD once every third day. The dose of the IMiD or the CELMoD may be increased or decreased throughout the induction phase as required.

[0122] In an example, the induction phase may comprise administration of the IMiD or the CELMoD at least one, at least two, at least three, at least four or at least five weeks prior to the start of the treatment phase. In an example, the induction phase may comprise administration of the IMiD or the CELMoD for at least one week prior to the start of the treatment phase. For example, the induction phase may comprise administration of lenalidomide once per day for at least one week.

[0123] In an example, the induction phase may comprise administration of the steroid to help reduce malignant cell proliferation to inhibit cytokine production and reduce the activity of nuclear factor kappa B, which are required for malignant plasma cell survival. In an example, the induction phase may comprise administration of the steroid twice per week. In an example, the induction phase may comprise administration of the steroid once per week (i.e. weekly). In another example, the induction phase may comprise administration of the steroid once every second week (i.e. fortnightly). The dose of the steroid may be increased or decreased throughout the induction phase as required.

[0124] In an example, the induction phase may comprise administration of the steroid at least one, at least two, at least three, at least four or at least five weeks prior to the start of the treatment phase. In an example, the induction phase may comprise administration of the steroid for at least one week prior to the start of the treatment phase. For example, the induction phase may comprise administration of dexamethasone at least one week prior to the start of the treatment phase.

[0125] In an example, the induction phase may comprise administration of the IMiD or the CELMoD about once per day, and the steroid about once per week at least one week prior to the start of the treatment phase.

[0126] In an example, the duration of the induction phase is at least one, at least two, at least three or at least four weeks. For example, the duration of the induction phase is at least one week.

Maintenance Phase

[0127] In certain examples, methods of the present disclosure comprise a maintenance phase. In an example, the maintenance phase follows a treatment phase. In an example, the maintenance phase comprises administration of an anti-KMA antibody once every second week (i.e. fortnightly). In an example, the maintenance phase comprises administration of the anti-KMA antibody once per month (i.e. monthly). For example, the maintenance phase comprises administration of the anti-KMA monthly for at least one, at least two, at least three, at least four, at least five, at least six, at least seven or at least eight weeks. In these examples, monthly administration can be referred to as a maintenance dose (i.e., maintenance phase; also known as a follow up phase).

[0128] In an example, the maintenance phase may comprise administration of the IMiD or the CELMoD once per day (i.e. once daily). In another example, the maintenance phase may comprise administration of the IMiD or the CELMoD once every second day. In another example, the maintenance phase may comprise administration of the IMiD or the CELMoD once every third day. The dose of the IMiD or the CELMoD may be increased or decreased throughout the maintenance phase as required. For example, the maintenance phase may comprise administration of lenalidomide once per day.

[0129] In one example, the dose of the IMiD may be stopped for a period of time as required (e.g., when trying to resolve a severe adverse event, such as a cytopenia). In another example, the dose of the IMiD may be delayed for a period of time as required.

[0130] In an example, the maintenance phase may comprise administration of the steroid once per week (i.e. weekly). In another example, the maintenance phase may comprise administration of the steroid once every second week (i.e. fortnightly). In another example, the maintenance phase may comprise administration of the steroid once every third week. In another example, the maintenance phase may comprise administration of the steroid once every fourth week. The dose of the steroid may be increased or decreased throughout the maintenance

phase as required. For example, the maintenance phase may comprise administration of dexamethasone once per week.

[0131] In an example, the maintenance phase may comprise administration of the anti-KMA antibody about once per month, the IMiD or the CELMoD about once per day, and the steroid about once per week.

[0132] In an example, the duration of the maintenance phase is at least 8, at least 9, at least 10, at least 11, at least 12, at least 13 or at least 14 weeks. For example, the duration of the maintenance phase is at least 12 weeks. In another example, the maintenance phase may be continued until disease progression (i.e. indefinitely).

Administration

[0133] The above referenced dosing regimen requires administration via various routes. Exemplary routes of administration include intravenous administration as a bolus, continuous infusion over a period of time, or oral administration. Those of skill in the art will appreciate that the most appropriate route of administration will be largely dependent on the treatment being administered. For example, an anti-KMA antibody can be administered intravenously.

[0134] In an example, the anti-KMA antibody is administered intravenously via a bolus. In an example, the anti-KMA antibody is administered intravenously via continuous infusion. In an example, intravenous infusion of an anti-KMA antibody lasts about one to two hours.

[0135] In an example, the IMiD or the CELMoD is administered orally. For example, these treatments may be administered orally via a tablet. In an example, the steroid is administered intravenously.

[0136] In an example, the anti-KMA antibody, the IMiD or the CELMoD and the steroid are administered as separate compositions. For example, the anti-KMA antibody, the IMiD or the CELMoD and the steroid can be administered sequentially. In this example, administration of the anti-KMA antibody, IMiD or CELMoD and steroid is carried out over a defined time period (usually hours or days). In an example, the period between sequential administration can be several days up to several weeks, provided that there is still sufficient levels of the first therapeutic to provide or add to the therapeutic benefit of the second or third therapeutic when it is administered.

[0137] In an example, the IMiD or the CELMoD and the steroid are administered via the same route. For example, both the IMiD or the CELMoD and the steroid can be administered orally. In an example, the IMiD or the CELMoD can be given as an oral drug at about 25 mg per day, once daily. For example, lenalidomide can be given orally at about 25 mg, once per

day. In an example, the steroid can be given as an oral drug at about 40 mg per day, once weekly. For example, dexamethasone can be given orally at about 25 mg, once per day.

[0138] In an example, dosing can be adjusted based on clinical evaluation or, if appropriate, prescribing information. Exemplary clinical evaluation may include physical examination, assessment of haematological toxicity (e.g. determining anaemia, neutropenia or thrombocytopenia).

Methods of Treatment

[0139] In one example, the present disclosure relates to a method of treating multiple myeloma in a subject in need thereof, the method comprising administering to the subject a treatment which comprises an anti-KMA antibody, an immunomodulatory drug (IMiD) or a cereblon E3 ligase modulator (CELMoD), and a steroid. For example, the methods can comprise administering the above referenced dosing regimen.

[0140] As used herein, the terms “treating”, “treat” or “treatment” include administering a therapeutically effective amount of an anti-KMA antibody, an IMiD or a CELMoD, and a steroid to reduce or delay the onset or progression of multiple myeloma, or to reduce or eliminate at least one symptom of multiple myeloma.

[0141] The terms “multiple myeloma” or “myeloma” or “MM” are used in the context of the present disclosure to refer to cancer of plasma cells. In the context of the present disclosure, these terms encompasses secretory myeloma, non-secretory myeloma, light chain only myeloma, smouldering myeloma and related pathologies. Exemplary related pathologies include plasmacytoma, amyloidosis, monoclonal gammopathy of undetermined significance.

[0142] In an example, the multiple myeloma is kappa type myeloma. For example, the multiple myeloma expresses KMA. In another example, the multiple myeloma expresses kappa light chain. In an example, the multiple myeloma expresses IgG Kappa. In a further example, the multiple myeloma expresses IgA Kappa.

[0143] Subjects with multiple myeloma can be characterised into various subject populations. Exemplary populations are described in Rajkumar et al. 2011.

[0144] In an example, a subject's multiple myeloma can be characterised as progressive disease (Rajkumar et al. 2011). Put another way, the methods of the present disclosure relate to the treatment of progressive multiple myeloma in a subject. Exemplary indicators of “progressive disease” include an increase of about 25% from the lowest response value in any one of the following: Serum M-component (e.g., absolute increase > or equal to 0.5 g/dL) and/or Urine M-component (e.g., absolute increase must be > or equal to 200 mg/24hr). Other

exemplary indicators include definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas; development of hypercalcemia (e.g., corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the multiple myeloma. In an example, the subject's multiple myeloma has relapsed and is characterised as progressive disease. In this example, the subject's multiple myeloma can also be refractory to therapy.

[0145] In another example, the subject has primary refractory myeloma. "Primary refractory myeloma" is used to refer to disease that is nonresponsive in subjects who have never achieved a minimal response or better with any therapy.

[0146] In another example, the subject has refractory myeloma. The term "refractory myeloma" is used to refer to disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. In an example, a subjects multiple myeloma is refractory to an anti-cancer therapy. The term "refractory" is used in this context to refer to a line of anti-cancer therapy that is no longer therapeutically effective against a subject's multiple myeloma.

[0147] In an example, the subject's multiple myeloma has relapsed. "Relapsed myeloma" is used to refer to previously treated myeloma that progresses and requires the initiation of salvage therapy but does not meet criteria for either "primary refractory myeloma" or "refractory myeloma".

[0148] In an example, a subject treated by the methods of the present disclosure can be refractory to at least one proteasome inhibitor. For example, a subject can be refractory to bortezomib. A "line of therapy" is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy.

[0149] In another example, subjects are refractory to at least two prior lines of therapy. In another example, a subject may be refractory to at least three, at least four, at least five or at least six prior lines of therapy. In this example, at least one line of therapy may be lenalidomide.

[0150] In another example, the subject has relapsed and refractory myeloma. "Relapsed and refractory myeloma" is used to refer to disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in subjects who have achieved minimal response (MR) or better at some point previously before then progressing in their disease course.

[0151] In an example, the multiple myeloma treated according to the present disclosure is characterised as stable disease at the time of first administration. Put another way, subjects can be in plateau phase at the time of first administration. Exemplary criteria for stable disease can include stabilization of the M-protein without further tumour regression despite continued treatment, few or no symptoms from myeloma and/or no blood transfusion requirement (Blade et al. 1998).

[0152] Subjects treated according to the methods of the present disclosure have multiple myeloma or a related pathology encompassed by the present disclosure.

[0153] In an example, a subject treated according to the present disclosure has received at least one line of prior therapy for their multiple myeloma. For example, a subject's multiple myeloma can have relapsed. In another example, a subject has received at least two, at least three, at least four, at least five or at least six prior lines of therapy. In these examples, a subject can have achieved at least a minimal response (e.g., about 25% reduction in M protein) to their most recent line of therapy.

[0154] In another example, a subject has serum kappa free light chain levels less than about 350 mg/ml. In another example, a subject has serum kappa free light chain levels less than about 300 mg/ml. In another example, a subject has serum kappa free light chain levels less than about 275 mg/ml. In another example, a subject has serum kappa free light chain levels less than about 250 mg/ml.

[0155] In another example, the methods of the present disclosure also relate to treating multiple myeloma in subjects with high serum cytokine levels. For example, the methods of the present disclosure relate to treating multiple myeloma in a subject, the method comprising selecting a subject who has high serum levels of one or more of the following factors relative to control serum levels: hepatocyte growth factor (HGF), macrophage inhibitory factor (MIF), CCL27, G-CSF, CXCL9, and CXCL10; and administering to the subject an anti-KMA antibody. In one aspect of the examples herein, serum analyte levels described herein are determined by immunoassay.

[0156] In an example, a high serum level of HGF is above about 0.5 ng/ml. In an example, a high serum level of HGF is above about 0.6 ng/ml, about 0.7 ng/ml, about 0.8 ng/ml, about 0.9 ng/ml, about 1.0 ng/ml, about 1.1 ng/ml, about 1.2 ng/ml, about 1.3 ng/ml, about 1.4 ng/ml or about 1.5 ng/ml. In another example, a high serum level of HGF is at least about 1.6 ng/ml. In another example, a high serum level of HGF is at least 1.6 ng/ml.

[0157] In another example, a high serum level of MIF is above about 5000 pg/ml. In another example, a high serum level of MIF is above about 5200 pg/ml, about 5400 pg/ml, about 5600

pg/ml, about 5800 pg/ml, about 6000 pg/ml, about 6200 pg/ml, about 6400 pg/ml, about 6600 pg/ml, about 6800 pg/ml or about 7200 pg/ml. In one example, a high serum level of MIF is above 5000 pg/ml.

[0158] In another example, a high serum level of CCL27 is above about 500 pg/ml. In another example, a high serum level of CCL27 is above about 600 pg/ml, about 700 pg/ml, about 800 pg/ml, about 900 pg/ml, about 1000 pg/ml, about 1100 pg/ml, about 1200 pg/ml, about 1300 pg/ml, about 1400 pg/ml or about 1500 pg/ml. In one example, a high serum level of CCL27 is above 500 pg/ml.

[0159] In another example, a high serum level of G-CSF is above about 55 pg/ml. In another example, a high serum level of G-CSF is above about 65 pg/ml, about 75 pg/ml, about 85 pg/ml, about 95 pg/ml, about 105 pg/ml, about 115 pg/ml, about 125 pg/ml, about 135 pg/ml, about 145 pg/ml or about 155 pg/ml. In one example, a high serum level of G-CSF is above 55 pg/ml.

[0160] In another example, a high serum level of CXCL9 is above about 550 pg/ml. In another example, a high serum level of CXCL9 is above about 600 pg/ml, about 650 pg/ml, about 700 pg/ml, about 750 pg/ml, about 800 pg/ml, about 850 pg/ml, about 900 pg/ml, about 950 pg/ml, about 1000 pg/ml or about 1050 pg/ml. In one example, a high serum level of CXCL9 is above 550 pg/ml.

[0161] In another example, a high serum level of CXCL10 is above about 850 pg/ml. In another example, a high serum level of CXCL10 is above about 900 pg/ml, about 950 pg/ml, about 1000 pg/ml, about 1050 pg/ml, about 1100 pg/ml, about 1150 pg/ml, about 1200 pg/ml, about 1250 pg/ml, about 1300 pg/ml or about 1350 pg/ml. In another example, a high serum level of CXCL10 is above 850 pg/ml.

[0162] High serum cytokine levels are determined in a sample obtained from the subject.

Additional steps

[0163] In another example, the methods of the present disclosure further comprise administering one or more additional agents or treatments. For example, anti-cancer agents, proteasome inhibitors or autologous stem cell transplantation. Exemplary anti-cancer agents include histone deacetylase inhibitors such as panobinostat or vorinostat, antibodies such as elotuzumab, daratumumab, isatuximab or anti-PD1 antibodies such as pembrolizumab, nivolumab and atezolizumab. Exemplary proteasome inhibitors include marizomib, oprozomib, epoxomicin, salinosporamide A, carfilzomib, ixazomib and bortezomib.

Autologous stem cell transplantation is the use of healthy blood stem cells from the subject's body to replace diseased or damaged bone marrow.

[0164] In an example, at least one additional agent is administered. For example, bortezomib can be administered. In other examples, at least two, at least three, at least four, at least five, at least six additional agents may be administered.

Kits

[0165] The combination dosing regimen according to the present disclosure can be provided in a kit or pack. For example, the therapeutic combination disclosed herein may be packaged in a suitable container with written instructions for treating an above referenced condition (e.g., multiple myeloma).

[0166] In an example, an anti-KMA antibody may be provided in a single dose or multiple doses. For example, the anti-KMA antibody may be provided in a single dose container such as a vial. In an example, the anti-KMA antibody may be provided in multiple single dose containers sufficient for at least 8 weeks of treatment. For example, the kit or pack may comprise at least 8 vials of pre-prepared KM.

[0167] In an example, an IMiD or a CELMoD may be provided in a single dose or multiple doses. For example, the IMiD or the CELMoD may be provided in a single dose container such as a pre-packaged pill. In an example, the IMiD or the CELMoD may be provided in multiple single dose containers sufficient for at least 8 weeks of treatment. For example, the kit or pack may comprise at least 60 pre-packaged pills of lenalidomide.

[0168] In an example, a steroid may be provided in a single dose or multiple doses. For example, the steroid may be provided in a single dose container such as a pre-packaged pill. In an example, the steroid may be provided in multiple single dose containers sufficient for at least 8 weeks of treatment. For example, the kit or pack may comprise at least 8 pre-packaged pills of dexamethasone.

[0169] The present disclosure includes the following non-limiting Examples.

EXAMPLES

EXAMPLE 1 – Materials and Methods

Early Investigational Plan

[0170] An early investigational study looking at four dose levels of KM (0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, 10 mg/kg) was undertaken. The assay data was taken up to Day 45 for

patients in these dose groups, and showed that KM could still be detected until at least Day 15, even at the lower doses. This early data suggested that anti-KMA antibodies were not subject to the phenomenon known as antigen sink, and as a result there was a higher probability that the anti-KMA antibody would be exposed to KMA cells without the need for higher dosage levels. As such, taken together with the known potential for monoclonal antibody induced immunotoxicity at higher doses, anti-KMA antibodies were considered good candidates for low dosing. Accordingly, the phase IIb study described below was designed based on these low doses.

Study Design

[0171] Phase IIb, multi-centre, open label sequential cohort study evaluating kappamab (KM) alone (KM, Stage 1) and then KM in combination with lenalidomide (LEN) and dexamethasone (DEX) (KM-Rd, Stage 2) in relapsed/refractory multiple myeloma (κ RRMM). Key inclusion criteria for both stages were progressive kappa-restricted multiple myeloma (κ MM) (as per International Myeloma Working Group (IMWG) criteria, Kumar et al. 2016), 1-3 prior lines of therapy and no prior LEN exposure.

Study stages, dosing and stopping criteria

[0172] Recruitment was planned for 60 patients in total, with an initial intention to treat 30 patients per stage. In Stage 1, patients received KM (10 mg/kg intravenous (IV) infusion) weekly for 8 weeks then every 4 weeks as maintenance. In Stage 2, KM dosing was as per Stage 1 with the addition of LEN, 25 mg Days 1-21 of each 28-day cycle and DEX 40 mg weekly, apart from Cycle 1 which was of 35 days duration (28-day cycles from Cycle 2 onwards) as patients commenced LEN for 21 days and DEX 1 week prior to starting KM (Figure 1). All patients received anti-viral, thromboembolic prophylaxis and osteolytic prophylaxis as per institutional practice. Treatment continued until unacceptable toxicity, progression, death or withdrawal of consent. Response rates and any adverse events (AEs) were periodically assessed.

Combination KM-Rd cohort compared to matched controls (Rd-MRDR)

[0173] The overall response rate (ORR), overall survival (OS) and progression free survival (PFS) of the KM-Rd cohort was compared to a contemporaneous control group of κ MM patients who had received Rd for RRMM (Rd-MRDR group), identified via the Australian and New Zealand Myeloma and Related Diseases Registry (MRDR) (www.mrdr.net)

au/), who were matched for age, gender and prior lines of therapy (**Table 3**). The patients also had a similar mix of types of prior therapies, number of prior lines and cytogenetic risk. The KM-Rd group had a higher percentage of patients with baseline ISS stage 2 diagnoses (55%) versus the MRDR cohort (45%) and the KM cohort (22%). Both the KM-Rd and MRDR cohorts had 26% of patients with ISS stage 3 at baseline, while the KM cohort had 33% who were ISS stage 3 at baseline. A limitation of this Rd-MRDR dataset was that patients had their disease status recorded only every 4 months, however an advantage of this dataset was that OS was regularly cross referenced with the Australian Institutes of Health and Welfare National Death Index (www.aishw.gov.au/about-our-data/our-data-collections/national-death-index). Importantly, both the KM-Rd cohort and the Rd MRDR controls were treated within the same time period and with similar supportive care and access to both reimbursed pomalidomide and carfilzomib but neither CD38 nor BCMA targeting immune therapies.

Study Endpoints

[0174] The primary endpoint for both Stage 1 and Stage 2 was the clinical benefit rate (CBR). The primary and secondary endpoints are summarised in Table 2. Patients were evaluated every 28 days for both OS and PFS while on study. Comparison of CBR, ORR, OS and PFS between KM-Rd and Rd-MRDR groups was done after the data cut-off. Assessment of duration of response (DoR) and time to next treatment (TTNT) was done in the KM-Rd group only; DoR and TTNT data were not available for the Rd-MRDR group.

Table 2. Study endpoints and definitions

Primary Endpoint	Definition
Clinical Benefit Rate (CBR)	Minimal response (MR) or better as per the IMWG uniform response criteria ¹¹
Secondary Endpoints	
Overall response rate (ORR)	The proportion of patients who achieved a $\geq$ partial response [PR] as per the IMWG uniform response criteria ¹¹
Safety Endpoints:	
Overall survival (OS)	Measured from the date of first dose of study drug until the date of death from any cause
Progression free survival (PFS)	Measured from the date of first dose of study drug until the earliest of the date of relapse, progression or death from any cause
Infusion-related Reactions (IRRs)	Symptoms of an IRR can include fever, chills, shakes, itching, rash, hyper- or hypotension, difficulty breathing, vomiting or headache.
Adverse Events (AEs)	Unintended changes in signs or symptoms of the body; incidence and severity of AEs were assessed using the CTCAE version 4.0.
Duration of response (DoR)	Restricted to patients who achieved PR, measured from the date on which a PR or better was first observed; patients who were not known to have progressed or died were censored at the date of their last evaluation

Time to next treatment (TTNT)	Measured from the date of first dose of study drug until the date that next therapy commenced or the date of death if another therapy did not commence, and, censored at the date of last contact
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Statistical Approach

[0175] Demographic and baseline characteristics were compared between the KM-Rd cohort and the Rd-MRDR controls using a Chi-squared test. CBR and ORR were estimated as simple percentages and 95% credible intervals (CI) were calculated as specified in the protocol using the pbeta and qbeta functions in R Version 4. A descriptive analysis of each of the time-to-event endpoints (DoR, TTNT, OS and PFS) in each stage used the Kaplan-Meier (product-limit) method to estimate the survival functions, with conventional 95% confidence intervals (CI) for the median survival time, DoR, TTNT, OS and PFS calculated using the Brookmeyer and Crowley method. Median potential follow-up was estimated by reversing the censor indicators in the Kaplan-Meier analyses. TTNT and the competing risk of death before a switch to another therapy were investigated by the calculation of cumulative incidence functions using the cmprsk library (Version 2.2-11) in R Version 4. The comparisons of the time-to-event endpoints comparing the KM cohort with KM-Rd cohort, and the KM-Rd cohort with the Rd-MRDR controls were undertaken using log-rank tests and were summarised as hazard ratios with 95% confidence intervals calculated using Cox proportional hazards regression models. These analyses were performed using SPSS v27 and Stata 16.1. A two-tailed p-value <0.05 was taken to indicate statistical significance.

EXAMPLE 2 – Clinical Assessment

Kappamab dose cohorts

[0176] Fifty-nine of the planned 60 patients were enrolled between November 2016 and July 2019. Demographics and baseline characteristics are described for Stage 1, Stage 2 and the Rd-MRDR patients in Table 3. Recruitment to Stage 1 (KM cohort) was terminated early (n=19), as the first PoC criterion was not met and posterior predictive probability calculations for CBR indicated that PoC was unlikely to be declared. Recruitment to Stage 2 (KM-Rd cohort) was expanded from 30 to 40 patients.

Table 3. Demographics and Baseline Characteristics

Factor	Stage 1 KM	Stage 2 KM-Rd	MRDR Rd Controls	p-value ¹
N	19	40	77	
Age, years (IQR)	60 (40 – 82)	68 (63 - 74)	69 (61 - 74)	NS
Time from diagnosis, months (IQR)		34 (18 - 47)	26 (17 - 38)	NS
Gender				NS
Male	58%	55%	55%	
Female	42%	45%	45%	
ISS at diagnosis				NS
1	44%	19%	29%	
2	22%	55%	45%	
3	33%	26%	26%	
Paraprotein type				<0.001
IgG	74%	50%	70%	
IgA	5%	25%	29%	
IgD	0%	0%	1%	
Light chain only	21%	25%	0%	
Prior lines of treatment				NS
1	42%	55%	39%	
2	47%	35%	44%	
3	11%	0%	2%	
4	0%	0%	4%	
5	0%	0%	1%	
Prior therapy				NS
PI	100%	93%	97%	
Refractory to PI	5%	18%	21%	
Thalidomide	47%	55%	50%	
ASCT	53%	53%	47%	
Cytogenetic risk ²				NS
Standard	89%	77%	83%	
High	11%	23%	18%	

¹Stage 2 versus Rd-MRDR controls; ²High risk = t(4;14), del17p or t(14;16); IQR = interquartile range

[0177] At the study censor date, two patients in Stage 2 (5%) remained on. In the other patients, reasons for discontinuation were progression (Stage 1 = 16/19 [84%], Stage 2 = 31/40 [70%]), withdrawal of consent unrelated to KM toxicity (Stage 1 = 3/19 [16%], Stage 2 = 4/40 [10%]), and toxicity due to LEN administration (Stage 2 = 3/40 [7.5%]). In Stage 2, two patients (5%) died on study from causes that were considered by the investigator to be not related to study drug (pneumonia, n = 1; unknown cause, n = 1).

Primary and secondary endpoints for Stage 1 and Stage 2

[0178] The CBR for Stage 1 and Stage 2 were 5% (95% CI: 0.5 – 21.1%) [1/19, PR=1] and 93% (95% CI: 79.9 – 97.3%) [37/40; CR=3/37 (8.1%), VGPR=11/37 (29.7%), PR=19/37 (51.4%), MR=4/37 (10.8%), respectively, with ORR 5% [1/19] and 83% (95% CI: 67.7 – 91.1%) [33/40], respectively. The median PFS for Stage 1 and Stage 2 was 2.0 months (95% CI: 0.0 – 4.7 months) and 12.7 months (95% CI 6.6 m to 18.8 months) (HR 0.25, 95% CI 0.13 to 0.47, $p < 0.001$), respectively, with median OS not reached for both stages. Median DoR and TTNT in Stage 2 were 12.9 months (95% CI 6.2 to 19.6 months) (Figure 2) and 21.9 months (95%CI 12.6 – 28.3 months), respectively. Moreover, for Stage 2 at 12 and 24 months the cumulative incidences of switching to another treatment were 27.5% (95% CI 13.5 to 43.5%) and 55.1% (35.3 to 71.1%) respectively and the cumulative incidence of death before a switch to another treatment remained at 8.8% (95% CI 2.2 – 21.6%) from 7.4 to 30.7 months (Figure 3).

Comparison of the Stage 2 KM-Rd and Rd-MRDR cohorts

[0179] Fifty-one of 77 patients (66%) in the Rd-MRDR cohort had response data available for both CBR and ORR (Table 4). KM-Rd was superior to Rd-MRDR – 93% versus 63% for CBR and 83% versus 45% for ORR respectively, both $p < 0.001$ (Figure 4). Seventy-five of 77 patients in the Rd-MRDR control group had data for survival with no difference in PFS between KM-Rd and Rd-MRDR – median PFS 12.7 months versus 10.3 months, 95% CI 6.23 to 23.57, $p = 0.55$ but with a significant OS advantage – median OS not reached vs 27.8 months, $p = 0.02$, HR 0.46 (95% CI 0.25 to 0.87) (Figure 5).

Table 4. Responses, CBR and ORR – Rd-MRDR Controls versus Stage 2 KM-Rd

Clinical Benefit Rate				
Group	N	%	p-value	Odds Ratio (95% CI)
Rd-MRDR n= 51	32	63	<0.001	7.3 (2.0 – 27.0)
Stage 2 (KM-Rd) n = 40	37	93		
Overall Response Rate				
Group	N	%	p-value	Odds Ratio (95% CI)
Rd-MRDR n = 51	23	45	<0.001	5.7 (2.1 – 15.4)
Stage 2 (KM-Rd) n = 40	33	83		

M Protein and serum free light chain (sFLC) data observations in Stage 1 and 2 patients

[0180] Figure 6 shows serum M protein and kappa free light chain (κFLC) data, for each Stage. Of note in Stage 1, a patient showed a disease response based on reduced M protein levels however, their sFLC increased. In addition, one FLC-only MM patient maintained decreased sFLC levels for 31 cycles of treatment. In Stage 2, the majority of patients responded to KM-Rd (Panel C). The median percent change from baseline for sFLC was elevated to Cycle 3 (i.e., following 9 doses), then it reduced and remained below baseline.

Safety

[0181] Surprisingly, KM demonstrated a highly favourable toxicity profile even when administered as combination therapy (KM-Rd). In Stage 1, 3/19 patients (15.8%) experienced an infusion related reaction (IRR), with one Grade 1 and two Grade 2 reactions. In Stage 2, 8 IRRs, 6 with the first infusion, were observed. There was 1 Grade 3 IRR and 7 Grade 12 IRRs and no patients discontinued treatment because of IRRs. In particular, the patient with the Grade 3 IRR recovered following hydrocortisone, salbutamol and loratadine administration in the clinic, prior to hospital admission for observation. There were no haematologic toxicities reported with KM, whereas the rates of anaemia (12.5%), neutropenia (32.5%) and thrombocytopenia (18%) seen in Stage 2 with KM-Rd were as expected with Rd administration (Table 5). The most frequently reported non-haematologic AEs were fatigue, insomnia, musculoskeletal pain, peripheral neuropathy and diarrhoea (Table 6).

Table 5. Stage 2 Haematologic AEs (N=40)

	Grade - N (%)				Total - N (%)
	1	2	3	4	
Neutropenia	2 (5%)	3 (7.5%)	6 (15%)	2 (5%)	13 (32.5%)
Anaemia	1 (2.5%)	1 (2.5%)	3 (7.5%)	0 (0%)	5 (12.5%)
Thrombocytopenia	1 (2.5%)	1 (2.5%)	2 (5%)	3 (7.5%)	7 (18%)

Table 6. Treatment Emergent Non-Haematologic AEs (≥ 10% in Stage 2)

Adverse Event	Stage 1		Stage 2	
	All grade, %	Grade 3, %	All Grade, %	Grade 3, %
Rash	16	-	10	-
Hyperglycaemia	-	-	10	-
Fatigue	32	-	30	3
Abdominal pain	5	-	10	3
Constipation	-	-	10	-

Diarrhoea	5	-	13	-
Nausea	-	-	10	-
Hypophosphatemia	-	-	10	-
Infusion related reaction	16	-	13	3
Peripheral Neuropathy	-	-	15	3
Insomnia	-	-	23	6
Cramps	-	-	10	-
Pain	5	-	20	-
URTI	5	-	20	-
Pneumonia	-	-	8	8
Cellulitis	10	5	10	-

[0182] The low incidence of KM-treatment related adverse events observed in clinical trials to date support doses of KM higher than 10 mg/kg in combination with immunomodulatory drug (IMiD)/cereblon E3 ligase modulator (CELMoD) and steroid therapy. Essentially, the KM-Rd safety profile recapitulated that seen with Rd (Dimopoulos et al. 2007; Weber et al. 2007) and with only infrequent (14%) and low-grade KM-related IRRs. The lack of increase in neutropenia and infection rates in the KM-Rd cohort relative to Rd administration in the literature likely reflects the highly restricted pattern of KMA expression, with KMA being found only on malignant plasma cells and limited numbers of tonsillar B-cells (Walker et al. 1985; Hutchinson et al. 2014).

[0183] It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

[0184] All publications discussed above are incorporated herein in their entirety.

[0185] Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

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CLAIMS:

1. A method of treating multiple myeloma in a subject in need thereof, the method comprising administering to the subject a treatment which comprises:
 - (i) at least 30 mg/kg of an anti-KMA antibody;
 - (ii) an immunomodulatory drug (IMiD) or cereblon E3 ligase modulator (CELMoD); and
 - (iii) a steroid.
2. The method according to claim 1, wherein the anti-KMA antibody comprises a V_H and a V_L, the V_H comprising a complementarity determining region (CDR) 1 comprising an amino acid sequence as shown in SEQ ID NO: 6, a CDR2 comprising an amino acid sequence as shown in SEQ ID NO: 7 and a CDR3 comprising a sequence as shown in SEQ ID NO: 8 and the V_L comprising a CDR 1 comprising an amino acid sequence as shown in SEQ ID NO: 9, a CDR2 comprising an amino acid sequence as shown in SEQ ID NO: 10 and a CDR3 comprising a sequence as shown in SEQ ID NO: 11.
3. The method according to claim 1 or 2, wherein the anti-KMA antibody has a heavy chain variable region (VH) comprising a sequence set forth in SEQ ID NO: 1 and a light chain variable region (VL) comprising a sequence set forth in SEQ ID NO: 2.
4. The method according to any one of claims 1 to 3, wherein the IMiD is lenalidomide, pomalidomide or thalidomide.
5. The method according to any one of claims 1 to 4, wherein the IMiD is lenalidomide.
6. The method according to any one of claims 1 to 3, wherein the CELMoD is iberdomide or CC-92480.
7. The method according to any one of claims 1 to 6, wherein about 25 mg of the IMiD or the CELMoD is administered to the subject.
8. The method according to any one of claims 1 to 7, wherein the steroid is dexamethasone or prednisone.

9. The method according to any one of claims 1 to 8, wherein the steroid is dexamethasone.
10. The method according to any one of claims 1 to 9, wherein about 40 mg of the steroid is administered to the subject.
11. The method according to any one of claims 1 to 10, wherein treatment comprises administering to the subject in a treatment phase:
 - (i) at least 30 mg/kg of the anti-KMA antibody once per week;
 - (ii) the IMiD or the CELMoD once per day; and
 - (iii) the steroid once per week.
12. The method according to claim 11, wherein the duration of the treatment phase is between at least 6 weeks and at least 10 weeks.
13. The method according to claim 11 or 12, further comprising administering to the subject the IMiD or the CELMoD once per day for at least 3 weeks prior to the start of the treatment phase.
14. The method according to any one of claims 11 to 13, further comprising administering a steroid to the subject at least 1 week prior to the start of the treatment phase.
15. The method according to any one of claims 1 to 14, wherein the subject's immune cells are maintained at levels corresponding with their immune cells prior to administration of the anti-KMA antibody.
16. The method according to any one of claims 11 to 14, wherein the subject's immune cells are maintained at levels corresponding with their immune cells after the treatment phase.
17. The method according to claim 15, wherein the subject's immune cells are one or more or all of red blood cells; white blood cells; and platelets.

18. The method according to any one of claims 11 to 17, further comprising a maintenance phase which comprises administering to the subject:
- (i) at least 30 mg/kg of the anti-KMA antibody once per month;
 - (ii) the IMiD or the CELMoD once per day; and
 - (iii) the steroid once per week,
- wherein the maintenance phase follows after the treatment phase.
19. The method according to claim 18, wherein the duration of the maintenance phase is at least 12 weeks.
20. The method according to claim 18 or 19, wherein the maintenance phase continues until disease progression.
21. The method according to any one of claims 1 to 20, wherein about 30 mg/kg of the anti-KMA antibody is administered to the subject.
22. The method according to any one of claims 1 to 21, wherein the anti-KMA antibody is formulated for intravenous infusion.
23. The method according to any one of claims 1 to 22, wherein the subject has received at least one, at least two, at least three, at least four, at least five or at least six prior lines of therapy.
24. The method according to any one of claims 1 to 23, wherein the subject achieved at least a minimal response (25% reduction in M protein) to their most recent line of therapy.
25. The method according to any one of claims 1 to 24, wherein the subject is refractory to at least one, at least two, at least three or at least four prior lines of therapy.
26. The method according to any one of claims 1 to 25, wherein the subject is refractory to at least one proteasome inhibitor, IMiD or CELMoD or autologous stem cell transplantation.

27. The method according to any one of claims 1 to 26, wherein the subject has relapsed myeloma.
28. The method according to any one of claims 1 to 27, wherein the subject's multiple myeloma has relapsed and is refractory to at least one proteasome inhibitor, IMiD or CELMoD or autologous stem cell transplantation.
29. The method according to any one of claims 1 to 12 and 14 to 27, wherein the subject has no prior exposure to the IMiD or the CELMoD.
30. A combination dosing regimen for use in the treatment of multiple myeloma in a subject comprising:
- (i) at least 30 mg/kg of an anti-KMA antibody;
 - (ii) an immunomodulatory drug (IMiD) or cereblon E3 ligase modulator (CELMoD); and
 - (iii) a steroid.
31. The combination dosing regimen according to claim 30, wherein about 25mg of the IMiD or the CELMoD is administered to the subject.
32. The combination dosing regimen according to claim 30 or 31, wherein about 40mg of the steroid is administered to the subject.
33. The combination dosing regimen according to any one of claims 30 to 32, wherein the combination is administered once per week in a treatment phase.
34. The combination dosing regimen according to any one of claims 30 to 33, wherein the treatment phase comprises administration of:
- (i) at least 30 mg/kg of the anti-KMA antibody once per week;
 - (ii) the IMiD or the CELMoD once per day; and
 - (iii) the steroid once per week.
35. The combination dosing regimen according to any one of claims 30 to 34, wherein the duration of the treatment phase is between at least 6 weeks and at least 10 weeks.

36. The combination dosing regimen according to any one of claims 30 to 35, further comprising administering to the subject the IMiD or the CELMoD once per day for at least 3 weeks prior to the start of the treatment phase.

37. The combination dosing regimen according to any one of claims 30 to 36, further comprising administering a steroid to the subject at least 1 week prior to the start of the treatment phase.

38. The combination dosing regimen according to any one of claims 30 to 37, further comprising a maintenance phase which comprises administering to the subject:

- (i) at least 30 mg/kg of the anti-KMA antibody once per month;
- (ii) the IMiD or the CELMoD once per day; and
- (iii) the steroid once per week,

wherein the maintenance phase follows after the treatment phase

39. A kit comprising:

- (i) a single dose or multiple doses of at least 30 mg/kg of an anti-KMA antibody;
- (ii) a single dose or multiple doses of an immunomodulatory drug (IMiD) or cereblon E3 ligase modulator (CELMoD);
- (iii) a single dose or multiple doses of a steroid;
- (iv) instructions for using the anti-KMA antibody, the IMiD or the CELMoD, and the steroid, for the treatment of multiple myeloma in a subject.