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(71) Applicant: **JANSSEN BIOTECH, INC.** [US/US]; 800/850 Ridgeview Drive, Horsham, Pennsylvania 19044 (US).

(72) Inventors: **KANE, Colleen M.**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US). **SMIT, Marie-Anne Damiette**; Archimedesweg 29, 2333 Leiden (NL). **HILDER, Brandi**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US). **TOLBERT, Jaszianne**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US).

(74) Agent: **LANE, David A.** et al.; JOHNSON & JOHNSON, One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933 (US).

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(54) Title: COMBINATION REGIMENS FOR TREATING MULTIPLE MYELOMA

(57) Abstract: Embodiments of the present invention relate to methods of treating multiple myeloma in a subject in need thereof by administering therapeutically effective combination regimens comprising a GPRC5DxCD3 bispecific antibody and one or more of pomalidomide, daratumumab or lenalidomide.

WO 2025/094085 A1

COMBINATION REGIMENS FOR TREATING MULTIPLE MYELOMA

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to United States Provisional Application Serial Number 63/594,804, filed October 31, 2023, United States Provisional Application Serial Number 63/607,918, filed December 8, 2023, United States Provisional Application Serial Number 63/621,741, filed January 17, 2024, United States Provisional Application Serial Number 63/654,497, filed May 31, 2024, and United States Provisional Application Serial Number 63/698,140, filed September 24, 2024, the entire contents of which are incorporated herein by reference in their entirety.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[0002] This application contains a sequence listing, which is submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on September 30, 2024, is named "258199061902 (JBI6857WOPCT1) Sequence Listing.xml" and is 25,473 bytes in size.

FIELD OF THE INVENTION

[0003] Methods of treating multiple myeloma are disclosed.

BACKGROUND OF THE INVENTION

[0004] Multiple myeloma (MM) is a cancer of the plasma cells. Mechanistically, multiple myeloma is characterized by production of monoclonal proteins (M-proteins) comprised of pathological immunoglobulins or fragments of such, which have lost their function. The proliferation of multiple myeloma cells leads to subsequent displacement from the normal bone marrow niche, while overproduction of M-proteins causes characteristic osteolytic lesions, increased susceptibility to infections, hypercalcemia, renal insufficiency or failure, and neurological complications.

[0005] Treatment options for multiple myeloma have improved over time and vary depending on the aggressiveness of the disease, underlying prognostic factors, physical condition of the patient, and existing comorbidities. Therapeutic options include proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), alkylating agents, monoclonal antibodies (mAbs), antibody drug conjugate, histone deacetylase inhibitor, nuclear protein export inhibitor, chimeric antigen receptor (CAR) T cell therapy and stem cell transplantation.

[0006] Despite these therapeutic achievements, the disease recurs and is associated with additional risk factors (e.g., comorbidities or increasing age), thus warranting the need for novel therapeutic approaches, such as new dosage and treatment regimens. In particular in the elderly population, for which stem cell transplantation is often not a viable option, and in patients with refractory disease who exhausted several therapies, multiple myeloma remains an incurable malignancy and an unmet medical need with significant morbidity and mortality. In particular, there remains a need for therapeutic regimens that achieve rapid, deep and durable clinical responses, while providing manageable safety profiles.

SUMMARY OF THE INVENTION

[0007] Embodiments of the present invention relate to combination regimens comprising a GPRC5DxCD3 bispecific antibody, such as talquetamab, for treatment of multiple myeloma.

[0008] An embodiment of the present invention provides a method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a combination therapy comprising a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody and a therapeutically effective amount of pomalidomide.

[0009] Another embodiment of the present invention provides a method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a combination therapy comprising a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody and a therapeutically effective amount of daratumumab.

[0010] Another embodiment of the present invention provides a method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a combination therapy comprising a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody and a therapeutically effective amount of daratumumab and a therapeutically effective amount of pomalidomide.

[0011] Another embodiment of the present invention provides a method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a combination therapy comprising a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody and a therapeutically effective amount of daratumumab and a therapeutically effective amount of lenalidomide.

[0012] In certain embodiments, the GPRC5DxCD3 bispecific antibody comprises a GPRC5D binding domain comprising the HCDR1 of SEQ ID NO: 4, the HCDR2 of SEQ ID NO: 5, the HCDR3 of SEQ ID NO: 6, the LCDR1 of SEQ ID NO: 7, the LCDR2 of SEQ ID

NO: 8 and the LCDR3 of SEQ ID NO: 9, and a CD3 binding domain comprising the HCDR1 of SEQ ID NO: 14, the HCDR2 of SEQ ID NO: 15, the HCDR3 of SEQ ID NO: 16, the LCDR1 of SEQ ID NO: 17, the LCDR2 of SEQ ID NO: 18 and the LCDR3 of SEQ ID NO: 19.

[0013] In certain embodiments, the GPRC5D binding domain comprises a heavy chain variable region (VH) having the amino acid sequence of SEQ ID NO: 10 and a light chain variable region (VL) having the amino acid sequence of SEQ ID NO: 11, and the CD3 binding domain comprises a heavy chain variable region (VH) having the amino acid sequence of SEQ ID NO: 20 and a light chain variable region (VL) having the amino acid sequence of SEQ ID NO: 21.

[0014] In certain embodiments, the GPRC5DxCD3 bispecific antibody is an IgG1, an IgG2, an IgG3 or an IgG4 isotype.

[0015] In certain embodiments, the GPRC5DxCD3 bispecific antibody is an IgG4 isotype.

[0016] In certain embodiments, the GPRC5DxCD3 bispecific antibody comprises one or more substitutions in its Fc region.

[0017] In certain embodiments, the GPRC5DxCD3 bispecific antibody is an IgG4 isotype and comprises Proline/Alanine/Alanine substitutions at amino acid positions 228/234/235, respectively, in its Fc region (according to EU index numbering).

[0018] In certain embodiments, the GPRC5DxCD3 bispecific antibody is an IgG4 isotype and comprises F405L and R409K substitutions in its Fc region (according to EU index numbering).

[0019] In certain embodiments, the Fc region of the GPRC5D binding arm comprises Proline/Alanine/Alanine substitutions at amino acid positions 228/234/235, respectively, in its Fc region (according to EU index numbering).

[0020] In certain embodiments, the Fc region of the CD3 binding arm comprises S228P, F234A, L235A, F405L, and R409K substitutions in its Fc region (according to EU index numbering).

[0021] In certain embodiments, the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having the amino acid sequence of SEQ ID NO: 23.

[0022] In certain embodiments, the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 90% identity to the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having at least 90% identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 90% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 90% identity to the amino acid sequence of SEQ ID NO: 23.

[0023] In certain embodiments, the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 95% identity to the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having at least 95% identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 95% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 95% identity to the amino acid sequence of SEQ ID NO: 23.

[0024] In certain embodiments, the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 98% identity to the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having at least 98% identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 98% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 98% identity to the amino acid sequence of SEQ ID NO: 23.

[0025] In certain embodiments, the GPRC5DxCD3 bispecific antibody is talquetamab.

[0026] In certain embodiments, the subject has relapsed or refractory multiple myeloma.

[0027] In certain embodiments, the subject has received at least two prior lines of therapy.

[0028] In certain embodiments, the subject has received at least three prior lines of therapy.

[0029] In certain embodiments, the subject has received at least four prior lines of therapy.

[0030] In certain embodiments, the subject has received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

[0031] In certain embodiments, the subject has received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

[0032] In certain embodiments, the method comprises subcutaneously administering treatment doses of the GPRC5DxCD3 bispecific antibody in an amount of either (i) 0.4 mg/kg weekly (QW), or (ii) 0.8 mg/kg bi-weekly (Q2W).

[0033] In certain embodiments, the method comprises subcutaneously administering to the subject one or more step-up doses of the GPRC5DxCD3 bispecific antibody prior to administering the first treatment dose of the GPRC5DxCD3 bispecific antibody.

[0034] In certain embodiments, the method comprises subcutaneously administering 2 or 3 step-up doses of the GPRC5DxCD3 bispecific antibody prior to subcutaneously administering the first treatment dose.

[0035] In certain embodiments, the method comprises subcutaneously administering step-up doses of 0.01 mg/kg and 0.06 mg/kg of the GPRC5DxCD3 bispecific antibody prior to subcutaneously administering a treatment dose.

[0036] In certain embodiments, the method comprises subcutaneously administering step-up doses of 0.01 mg/kg, 0.06 mg/kg and 0.4 mg/kg of the GPRC5DxCD3 bispecific antibody prior to subcutaneously administering a treatment dose.

[0037] In certain embodiments, the method comprises subcutaneously administering step-up doses of the GPRC5DxCD3 bispecific antibody 2-4 days apart from each other.

[0038] In certain embodiments, the method comprises orally administering the pomalidomide in an amount of 2 mg daily or 4 mg daily.

[0039] In certain embodiments, the combination therapy comprises sequential 28-day treatment cycles.

[0040] In certain embodiments, the pomalidomide is administered in an amount of 2 mg daily or 4 mg daily for Days 1-21 of each pomalidomide treatment cycle.

[0041] In certain embodiments, the combination therapy comprises sequential 28-day treatment cycles; administration of the GPRC5DxCD3 bispecific antibody starts in Cycle 1; and administration of the pomalidomide starts in Cycle 2.

[0042] In certain embodiments, the combination therapy comprises sequential 28-day treatment cycles; Cycle 1 is a step-up phase comprising administration of one or more step-up doses and one or more treatment doses of the GPRC5DxCD3 bispecific antibody; and each subsequent treatment cycle (Cycle 2 onward) comprises oral administration of the pomalidomide in an amount of 2 mg daily on Days 1-21; and subcutaneous administration of the GPRC5DxCD3 bispecific antibody in an amount of either (i) 0.4 mg/kg weekly (QW), or (ii) 0.8 mg/kg bi-weekly (Q2W).

[0043] In certain embodiments, the combination therapy comprises sequential 28-day treatment cycles; Cycle 1 is a step-up phase comprising administration of a first step-up dose of 0.01 mg/kg, a second step-up dose of 0.06 mg/kg, a third step-up dose of 0.4 mg/kg, and a

first treatment dose of 0.8 mg/kg of the GPRC5DxCD3 bispecific antibody; and each subsequent treatment cycle (Cycle 2 onward) comprises oral administration of the pomalidomide in an amount of 2 mg daily on Days 1-21; and subcutaneous administration of the GPRC5DxCD3 bispecific antibody in an amount of 0.8 mg/kg bi-weekly (Q2W) (e.g., on Days 1 and 15).

[0044] In certain embodiments, the subject achieves a clinical response that is a partial response, a very good partial response, a complete response, or a stringent complete response.

[0045] All methods described herein, however expressed, may be described as corresponding uses, in particular medical uses.

BRIEF DESCRIPTION OF THE FIGURES

[0046] The following figures form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these figures in combination with the description of specific embodiments presented herein.

[0047] **FIG. 1** provides a schematic summary of the MonumenTAL-2 Phase 1b study design.

[0048] **FIG. 2** provides a summary of the patient characteristics of the Tal + Pom cohort of the MonumenTAL-2 Phase 1b study.

[0049] **FIG. 3** provides a summary of the overall response rate in patients from the Tal + Pom cohort of the MonumenTAL-2 Phase 1b study.

[0050] **FIG. 4** provides a schematic overview of MonumenTAL-6, a Phase 3 Randomized Study Comparing Talquetamab in Combination with Pomalidomide (Tal-P), Talquetamab in Combination with Teclistamab (Tal-Tec), and Investigator's Choice of Either Elotuzumab, Pomalidomide, and Dexamethasone (EPd) or Pomalidomide, Bortezomib, and Dexamethasone (PVd) in Participants with Relapsed or Refractory Myeloma who Have Received 1 to 4 Prior Lines of Therapy Including an Anti-CD38 Antibody and Lenalidomide.

[0051] **FIG. 5a** provides a table summary of pretreatment medication dosing schedules for Arm A (Tal-P) of the Phase 3 MonumenTAL-6 clinical study.

[0052] **FIG. 5b** provides a table summary of the initial study treatment dosing schedules for Arm A (Tal-P) of the Phase 3 MonumenTAL-6 clinical study, which were later updated.

[0053] **FIG. 5c** provides a table summary of the updated study treatment dosing schedules for Arm A (Tal-P) of the Phase 3 MonumenTAL-6 clinical study.

[0054] **FIG. 6a** provides a table summary of pretreatment medication dosing schedules for Arm C (EPd) of the Phase 3 MonumenTAL-6 clinical study.

[0055] **FIG. 6b** provides a table summary of study treatment dosing schedules for Arm C (EPd) of the Phase 3 MonumenTAL-6 clinical study.

[0056] **FIG. 6c** provides a table summary of study treatment dosing schedules for Arm C (PVd) of the Phase 3 MonumenTAL-6 clinical study.

[0057] **FIG. 7** illustrates overall response rate (ORR) from the Phase 1b MonumenTAL-2 clinical study.

DETAILED DESCRIPTION OF THE INVENTION

[0058] The disclosed methods can be understood more readily by reference to the following detailed description. It is to be understood that the disclosed methods are not limited to the specific methods described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed methods. All patents, published patent applications and publications cited herein are incorporated by reference as if set fourth fully herein.

[0059] As used herein, the singular forms "a," "an," and "the" include the plural.

[0060] Various terms relating to aspects of the description are used throughout the specification and claims. Such terms are to be given their ordinary meaning in the art unless otherwise indicated. Other specifically defined terms are to be construed in a manner consistent with the definitions provided herein.

[0061] "**About**" when used in reference to numerical ranges, cutoffs, or specific values means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. Unless explicitly stated otherwise within the Examples or elsewhere in the Specification in the context of an assay, result or embodiment, "about" means within one standard deviation per the practice in the art, or a range of up to 5%, whichever is larger.

[0062] "**Antibodies**" is meant in a broad sense and includes immunoglobulin molecules including monoclonal antibodies including murine, human, humanized and chimeric monoclonal antibodies, antigen binding fragments, multispecific antibodies, such as bispecific, trispecific, tetraspecific etc., dimeric, tetrameric or multimeric antibodies, single chain antibodies, domain antibodies and any other modified configuration of the

immunoglobulin molecule that comprises an antigen binding site of the required specificity. "Full length antibodies" are comprised of two heavy chains (HC) and two light chains (LC) inter-connected by disulfide bonds as well as multimers thereof (e.g. IgM). Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region (comprised of domains CH1, hinge, CH2 and CH3). Each light chain is comprised of a light chain variable region (VL) and a light chain constant region (CL). The VH and the VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with framework regions (FR). Each VH and VL is composed of three CDRs and four FR segments, arranged from amino-to-carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. Immunoglobulins can be assigned to five major classes, IgA, IgD, IgE, IgG and IgM, depending on the heavy chain constant domain amino acid sequence. IgA and IgG are further sub-classified as the isotypes IgA1, IgA2, IgG1, IgG2, IgG3 and IgG4. Antibody light chains of any vertebrate species can be assigned to one of two clearly distinct types, namely kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

[0063] "**Antigen binding fragment**" or "**antigen binding domain**" refers to a portion of an immunoglobulin molecule that binds an antigen. Antigen binding fragments can be synthetic, enzymatically obtainable or genetically engineered polypeptides and include the VH, the VL, the VH and the VL, Fab, F(ab')2, Fd and Fv fragments, domain antibodies (dAb) consisting of one VH domain or one VL domain, shark variable IgNAR domains, camelized VH domains, minimal recognition units consisting of the amino acid residues that mimic the CDRs of an antibody, such as FR3-CDR3-FR4 portions, the HCDR1, the HCDR2 and/or the HCDR3 and the LCDR1, the LCDR2 and/or the LCDR3. VH and VL domains can be linked together via a synthetic linker to form various types of single chain antibody designs where the VH/VL domains can pair intramolecularly, or intermolecularly in those cases when the VH and VL domains are expressed by separate single chain antibody constructs, to form a monovalent antigen binding site, such as single chain Fv (scFv) or diabody; described for example in Int. Patent Publ. Nos. WO1998/44001, WO1988/01649, WO1994/13804 and WO1992/01047.

[0064] "**Bispecific**" refers to an antibody that specifically binds two distinct antigens or two distinct epitopes within the same antigen. The bispecific antibody can have cross-reactivity to other related antigens, for example to the same antigen from other species (homologs), such as human or monkey, for example *Macaca cynomolgus* (cynomolgus, cyno)

or *Pan troglodytes*, or can bind an epitope that is shared between two or more distinct antigens.

[0065] "**Cancer**" refers to a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth results in the formation of malignant tumors that invade neighboring tissues and can also metastasize to distant parts of the body through the lymphatic system or bloodstream. A "cancer" or "cancer tissue" can include a tumor.

[0066] "**CD3**" refers to a human antigen which is expressed on T cells as part of the multimolecular T cell receptor (TCR) complex and which consists of a homodimer or heterodimer formed from the association of two or four receptor chains: CD3 epsilon, CD3 delta, CD3 zeta and CD3 gamma. Human CD3 epsilon comprises the amino acid sequence of SEQ ID NO: 2. SEQ ID NO: 3 shows the extracellular domain of CD3 epsilon.

SEQ ID NO: 2

MQSGTHWRVLGLCLLSVGVWGQDGNEEMGGITQTPYKVSISGTTVILTCPQYPG
SEILWQHNDKNIGGDEDDKNIGSDEDHLSLKEFSELEQSGYYVCYPRGSKPEDAN
FYLYLRARVCENCMEMDVMSVATIVIVDICITGGLLLLVYYWSKNRKAKAKPVT
RGAGAGGRQRGQNKERPPPVPNPDYEPIRKGQRDLYSGLNQRRI

SEQ ID NO: 3

DGNEEMGGITQTPYKVSISGTTVILTCPQYPGSEILWQHNDKNIGGDEDDKNIGSD
EDHLSLKEFSELEQSGYYVCYPRGSKPEDANFYLYLRARVCENCMEMD

[0067] "**CH3 region**" or "**CH3 domain**" refers to the CH3 region of an immunoglobulin. The CH3 region of human IgG1 antibody corresponds to amino acid residues 341-446. However, the CH3 region can also be any of the other antibody isotypes as described herein.

[0068] "**Combination**" means that two or more therapeutics are administered to a subject together in a mixture, concurrently as single agents or sequentially as single agents in any order.

[0069] **"Combination therapy,"** also referred to as **"combination regimen,"** as used herein refers to a therapeutically effective regimen that comprises administration of two or more anti-multiple myeloma therapeutic agents to a subject to treat multiple myeloma. The two or more therapeutics are administered to a subject on each therapeutic's respective dosing schedule over a time period (e.g., a time period may comprise one or more treatment cycles, such as one or more 28-day treatment cycles); for example, a combination therapy may comprise administering to a subject (i) "therapeutic #1" on its weekly or bi-weekly or

monthly dosing schedule starting on Day 1 of a treatment cycle and (ii) "therapeutic #2" on its weekly or bi-weekly or monthly dosing schedule starting on Day 1 of the same treatment cycle or a subsequent treatment cycle.

[0070] "**Complementarity determining regions"** (CDR) are antibody regions that bind an antigen. CDRs can be defined using various delineations such as Kabat (Wu et al. J Exp Med 132: 211-50, 1970) (Kabat *et al.,* Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991), Chothia (Chothia et al. J Mol Biol 196: 901-17, 1987), IMGT (Lefranc et al. Dev Comp Immunol 27: 55-77, 2003) and AbM (Martin and Thornton J Bmol Biol 263: 800-15, 1996). The correspondence between the various delineations and variable region numbering are described (see e.g. Lefranc et al. Dev Comp Immunol 27: 55-77, 2003; Honegger and Pluckthun, J Mol Biol 309:657-70, 2001; International ImMunoGeneTics (IMGT) database; Web resources, http://www_imgt_org). Available programs such as abYsis by UCL Business PLC can be used to delineate CDRs. The term "CDR", "HCDR1", "HCDR2", "HCDR3", "LCDR1", "LCDR2" and "LCDR3" as used herein includes CDRs defined by any of the methods described supra, Kabat, Chothia, IMGT or AbM, unless otherwise explicitly stated in the specification. Preferably, the term "CDR", "HCDR1", "HCDR2", "HCDR3", "LCDR1", "LCDR2" and "LCDR3" as used herein includes CDRs defined by the method of Kabat.

[0071] "**Comprising**" is intended to include examples encompassed by the terms "consisting essentially of" and "consisting of"; similarly, the term "consisting essentially of" is intended to include examples encompassed by the term "consisting of." Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

[0072] "**Fc gamma receptor**" (**FcγR**) refers to well-known FcγRI, FcγRIIa, FcγRIIb or FcγRIII. Activating FcγR includes FcγRI, FcγRIIa and FcγRIII.

[0073] "**GPRC5DxCD3 bispecific antibody**" refers to a bispecific antibody that specifically binds GPRC5D and CD3.

[0074] "**Human antibody**" refers to an antibody that is optimized to have minimal immune response when administered to a human subject. Variable regions of human antibody are derived from human immunoglobulin sequences. If human antibody contains a constant region or a portion of the constant region, the constant region is also derived from human

immunoglobulin sequences. Human antibody comprises heavy and light chain variable regions that are "derived from" sequences of human origin if the variable regions of the human antibody are obtained from a system that uses human germline immunoglobulin or rearranged immunoglobulin genes. Such exemplary systems are human immunoglobulin gene libraries displayed on phage, and transgenic non-human animals such as mice or rats carrying human immunoglobulin loci. "Human antibody" typically contains amino acid differences when compared to the immunoglobulins expressed in humans due to differences between the systems used to obtain the human antibody and human immunoglobulin loci, introduction of somatic mutations or intentional introduction of substitutions into the frameworks or CDRs, or both. Typically, "human antibody" is at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical in amino acid sequence to an amino acid sequence encoded by human germline immunoglobulin or rearranged immunoglobulin genes. In some cases, "human antibody" can contain consensus framework sequences derived from human framework sequence analyses, for example as described in Knappik et al., (2000) J Mol Biol 296:57-86, or synthetic HCDR3 incorporated into human immunoglobulin gene libraries displayed on phage, for example as described in Shi et al., (2010) J Mol Biol 397:385-96, and in Int. Patent Publ. No. WO2009/085462. Antibodies in which at least one CDR is derived from a non-human species are not included in the definition of "human antibody".

[0075] "**Humanized antibody**" refers to an antibody in which at least one CDR is derived from non-human species and at least one framework is derived from human immunoglobulin sequences. Humanized antibody can include substitutions in the frameworks so that the frameworks can not be exact copies of expressed human immunoglobulin or human immunoglobulin germline gene sequences.

[0076] **"Identity"** refers to a relationship between the sequences of two or more polypeptide molecules or two or more nucleic acid molecules, as determined by aligning and comparing the sequences. "Percent (%) sequence identity" with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for

instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, or MEGALIGN (DNAStar, Inc.) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

[0077] "**Isolated**" refers to a homogenous population of molecules (such as synthetic polynucleotides or a protein such as an antibody) which have been substantially separated and/or purified away from other components of the system the molecules are produced in, such as a recombinant cell, as well as a protein that has been subjected to at least one purification or isolation step. "Isolated antibody" refers to an antibody that is substantially free of other cellular material and/or chemicals and encompasses antibodies that are isolated to a higher purity, such as to 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% purity.

[0078] "**Monoclonal antibody**" refers to an antibody obtained from a substantially homogenous population of antibody molecules, i.e., the individual antibodies comprising the population are identical except for possible well-known alterations such as removal of C-terminal lysine from the antibody heavy chain or post-translational modifications such as amino acid isomerization or deamidation, methionine oxidation or asparagine or glutamine deamidation. Monoclonal antibodies typically bind one antigenic epitope. A bispecific monoclonal antibody binds two distinct antigenic epitopes. Monoclonal antibodies can have heterogeneous glycosylation within the antibody population. Monoclonal antibody can be monospecific or multispecific such as bispecific, monovalent, bivalent or multivalent.

[0079] "**Mutation**" refers to an engineered or naturally occurring alteration in a polypeptide or polynucleotide sequence when compared to a reference sequence. The alteration can be a substitution, insertion or deletion of one or more amino acids or polynucleotides.

[0080] "**Negative minimal residual disease status**" or "negative MRD status" or "MRD negative" refers to the PerMillionCount (i.e., a point estimate of malignant myeloma cells per million nucleated cells) in a patients on-study bone marrow sample relative to their reference bone marrow sample (i.e., talquetamab treatment naïve bone marrow sample). Based on this PerMillionCount, each sample is determined to be positive or negative. Samples are positive if the PerMillionCount is greater than or equal to the limit of sensitivity, otherwise they are negative. Negative minimal residual disease status can be determined at a sensitivity of

0.01% (10^{-4}), 0.001% (10^{-5}) or 0.0001% (10^{-6}). Negative minimal residual disease status was determined using next generation sequencing (NGS).

[0081] "**Pharmaceutical composition**" refers to composition that comprises an active ingredient and a pharmaceutically acceptable carrier.

[0082] "**Pharmaceutically acceptable carrier**" or "**excipient**" refers to an ingredient in a pharmaceutical composition, other than the active ingredient, which is nontoxic to a subject.

[0083] "**Recombinant**" refers to DNA, antibodies and other proteins that are prepared, expressed, created or isolated by recombinant means when segments from different sources are joined to produce recombinant DNA, antibodies or proteins.

[0084] "**Refractory**" refers to a cancer that is not amendable to surgical intervention and is initially unresponsive to therapy.

[0085] "**Relapsed**" refers to a cancer that responded to treatment but then returns.

[0086] "**Step-up dose**" refers to a dose of an active agent that is administered to a subject prior to a treatment dose. A step-up dose is lower than the treatment dose. To prevent or lessen certain toxicities, such as cytokine release syndrome (CRS), a "priming" dose strategy may include one or more lower step-up dose(s) followed by higher treatment doses. A "step-up phase" refers to an initial phase of a therapeutically effective regimen in which at least one step-up dose of a therapeutic is administered to the subject. A step-up phase may also include one or more treatment doses, *i.e.*, a step-up phase may include one or more step-up doses followed by one or more treatment doses; for example, a step-up phase may include two step-up doses followed by two treatment doses, or three step-up doses followed by one treatment dose. In particular embodiments, the step-up phase is 28 days, *i.e.*, the step-up phase is a 28-day cycle of a therapeutically effective regimen.

[0087] "**Subject**" includes any human or nonhuman animal. "Nonhuman animal" includes all vertebrates, e.g., mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, chickens, amphibians, reptiles, etc. Except when noted, the terms "patient" or "subject" are used interchangeably.

[0088] "**T cell redirecting therapeutic**" refers to a molecule containing two or more binding regions, wherein one of the binding regions specifically binds a cell surface antigen on a target cell or tissue and wherein a second binding region of the molecule specifically binds a T cell antigen. Examples of cell surface antigen include a tumor associated antigen, such as GPRC5D. Examples of T cell antigen include, e.g., CD3. This dual/multi-target

binding ability recruits T cells to the target cell or tissue leading to the eradication of the target cell or tissue.

[0089] "**Therapeutically effective amount**" refers to an amount effective, at doses and for periods of time necessary, to achieve a desired therapeutic result. A therapeutically effective amount can vary depending on factors such as the disease state, age, sex, and weight of the individual, and the ability of a therapeutic or a combination of therapeutics to elicit a desired response in the individual. Exemplary indicators of an effective therapeutic or combination of therapeutics that include, for example, improved well-being of the patient.

[0090] "**Treat**" or "treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder. Beneficial or desired clinical results include alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if a subject was not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

[0091] "**Treatment dose**" – refers to a dose of the active agent that is administered to a subject to treat a disease. A treatment dose may be administered at a regular dosing interval on a repetitive basis (e.g. weekly, biweekly, monthly). A treatment dose may be preceded by one or more step-up doses.

[0092] A patient that is "**triple-class exposed**" refers to a patient diagnosed with multiple myeloma (MM) that has previously been treated with (at a minimum) a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

[0093] "**Tumor cell**" or a "cancer cell" refers to a cancerous, pre-cancerous or transformed cell, either *in vivo*, *ex vivo*, or in tissue culture, that has spontaneous or induced phenotypic changes. These changes do not necessarily involve the uptake of new genetic material. Although transformation can arise from infection with a transforming virus and incorporation of new genomic nucleic acid, uptake of exogenous nucleic acid or it can also arise spontaneously or following exposure to a carcinogen, thereby mutating an endogenous gene. Transformation/cancer is exemplified by morphological changes, immortalization of cells, aberrant growth control, foci formation, proliferation, malignancy, modulation of tumor

specific marker levels, invasiveness, tumor growth in suitable animal hosts such as nude mice, and the like, *in vitro*, *in vivo*, and *ex vivo*.

[0094] The numbering of amino acid residues in the antibody constant region throughout the specification is according to the EU index as described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991), unless otherwise explicitly stated. Antibody constant chain numbering can be found for example at ImMunoGeneTics website, at IMGT Web resources at IMGT Scientific charts.

[0095] Conventional one and three-letter amino acid codes are used herein as shown in Table 1.

Table 1.

Amino acid	Three-letter code	One-letter code
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartate	Asp	D
Cysteine	Cys	C
Glutamate	Gln	E
Glutamine	Glu	Q
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

GPRC5DxCD3 bispecific antibodies and uses thereof

[0096] It is well-known in the art that drug development is an unpredictable field. The lack of predictability in the art is evidenced, for example, by health authority requirements (such as those of the Food and Drug Administration) to establish a safe and effective dosing regimen for each individual drug candidate in clinical trials. Over the last decade (2011-2020), only 7.9% of all developmental drug candidates achieved FDA approval from a Phase I clinical study. See Clinical Development Success Rates and Contributing Factors 2011-

2020. The rate of success is even lower in oncology, such that only 5.3% of oncology drug candidates succeed.

[0097] In the field of oncology, even for a drug that already has an established dose in a particular indication, the Food and Drug Administration (FDA) recommends further clinical studies to identify an optimal dose for a new indication; otherwise, patients may be exposed to unreasonable and significant risk, among other potential deficiencies. *See, e.g.,* Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases; Draft Guidance for Industry; January 2023).

[0098] In patients with relapsed or refractory disease who have exhausted several therapies, multiple myeloma remains an incurable malignancy and an unmet medical need with significant morbidity and mortality. The present inventors have developed novel combination regimens comprising GPRC5DxCD3 bispecific antibodies , e.g., combination regimens comprising GPRC5DxCD3 bispecific antibodies and pomalidomide (pom), that provide deep and durable efficacy.

[0099] For patients whose myeloma relapses after exposure to daratumumab and lenalidomide in the first or subsequent lines of therapy, treatment options are limited. In a retrospective review of patients who were refractory to anti-CD38 therapy and who received subsequent therapy after progression on PI, IMiD, and anti-CD38 therapy, the observed efficacy of the next treatment after was dismal, regardless of the salvage therapy chosen. Therefore, there remains a significant and critical unmet need for new therapeutic options directed at alternative mechanisms of action that can better control the disease, provide deeper, more sustained responses, and better long-term outcomes including maintenance of Health-related Quality of Life (HRQoL). The present inventors have developed novel combination regimens comprising a GPRC5DxCD3 bispecific antibody (e.g., talquetamab), pomalidomide (pom) and dexamethasone that provide deep and durable efficacy.

[0100] The inventors have further discovered that adverse events (AEs) associated with the GPRC5D target, such as oral toxicity (e.g., ageusia, dysgeusia, dry mouth, and/or dysphagia), and nail toxicity (e.g., nail disorder), and skin toxicity (e.g., dry skin, skin exfoliation, and/or pruritus) can be mitigated by dosing schedules that comprise less frequent dosing of talquetamab, while still achieving efficacious responses. It was also discovered that sufficient exposure to talquetamab, and minimal time to best response, can be achieved after about four 28-day treatment cycles, in accordance with dosing schedules described

herein, so that patients can experience reduced AEs while still having deep and durable responses and minimal amount of time to clinical response.

[0101] Monthly (Q4W) dosing of talquetamab was selected based on the pharmacokinetic (PK), pharmacodynamic, safety, and efficacy findings from a subset of the pivotal RP2D population in the MonumtanTAL-1 clinical study who switched to less frequent dosing, the Phase 1b TriMM-2 clinical study (combination therapy in relapsed/refractory populations), and early data from MonumenTAL-2 (combination therapy in relapsed/refractory populations). In those studies, TEAEs were tolerable and manageable; CRS was generally low grade and neurotoxicity events were rare. Additionally, data from MonumenTAL-1 demonstrates that participants who switched to less frequent dosing after achieving response with talquetamab monotherapy have improved progression-free survival (PFS) compared with the overall pivotal population and experienced fewer study drug-related TEAEs and Grade 3 or 4 TEAEs after switching and experienced improve resolution of on-target-related toxicity (e.g., oral, skin, and rash AEs). Overall, data from MonumanTAL-1 in which participants are receiving Q4W dosing demonstrated maintenance of response following switch, with a trend for improved resolution of GPRC5D-related oral, skin (rash and non-rash), and nail toxicities.

[0102] PK simulations showed that talquetamab trough levels following the first 0.8 mg/kg SC administration were comparable or higher than the maximum EC_{90} values identified in an ex vivo cytotoxicity assay. This assay assessed the ability of talquetamab to induce killing using mononuclear cells from the bone marrow samples of multiple myeloma patients in co-culture with T cells from healthy donors. The trough concentrations at steady state were also comparable to or higher than the maximum EC_{90}. It is believed that embodiments of the Q4W dosing schedule disclosed herein would maintain talquetamab's efficacy by balancing maximal reduction of disease burden with biweekly dosing in the initial 6 cycles of treatment with participant convenience and reduced exposure with Q4W dosing from Cycle 7 onward for participants with response of confirmed PR or better (or as early as Cycle 5 for participants who have achieved a confirmed response of VGPR or better).

Combination Regimens Comprising a GPRC5DxCD3 Bispecific Antibody and Pomalidomide

[0103] According to certain embodiments, combination regimens of the present invention (e.g., talquetamab, pomalidomide and dexamethasone) improve median progression free

survival (PFS) in a population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said reference population having been administered either (i) elotuzumab, pomalidomide, and dexamethasone (EPd) or (ii) pomalidomide, bortezomib, and dexamethasone (PVd). PFS refers to the duration from the date of treatment start to either progressive disease or death, whichever comes first.

[0104] According to certain embodiments, combination regimens of the present invention (e.g., talquetamab, pomalidomide and dexamethasone) improve overall response rate (ORR) in a population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, wherein the improvement in ORR is relative to ORR of a reference population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said reference population having been administered either (i) elotuzumab, pomalidomide, and dexamethasone (EPd) or (ii) pomalidomide, bortezomib, and dexamethasone (PVd). ORR refers to the percentage of subjects with best overall response of partial response (PR) or better according to international myeloma working group (IMWG) response criteria.

[0105] According to certain embodiments, combination regimens of the present invention (e.g., talquetamab, pomalidomide and dexamethasone) improve Complete Response (CR) or Better Rate in a population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, wherein the improvement in CR or Better Rate is relative to CR or Better Rate of a reference population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said reference population having been administered either (i) elotuzumab, pomalidomide, and dexamethasone (EPd) or (ii) pomalidomide, bortezomib, and dexamethasone (PVd). CR or better rate refers to the percentage of subjects with best overall response of CR or better according to IMWG response criteria.

[0106] According to certain embodiments, combination regimens of the present invention (e.g., talquetamab, pomalidomide and dexamethasone) improve Very Good Partial Response (VGPR) or Better Rate in a population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, wherein the improvement in VGPR or Better Rate is relative to VGPR or Better Rate of a reference population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said reference population having been administered either (i) elotuzumab, pomalidomide, and dexamethasone (EPd) or (ii) pomalidomide, bortezomib, and dexamethasone (PVd). VGPR or better rate refers to the percentage of subjects with best overall response of VGPR or better according to IMWG response criteria.

[0107] According to certain embodiments, combination regimens of the present invention (e.g., talquetamab, pomalidomide and dexamethasone) improve Minimal Residual Disease (MRD)-negative CR Rate in a population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, wherein the improvement in MRD-negative CR Rate is relative to MRD-negative CR Rate of a reference population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said reference population having been administered either (i) elotuzumab, pomalidomide, and dexamethasone (EPd) or (ii) pomalidomide, bortezomib, and dexamethasone (PVd). MRD-negative CR refers to the percentage of subjects who achieve both CR or better and MRD negativity at a threshold of 10^-5 at any timepoint after the date of randomization and before disease progression or start of subsequent antimyeloma therapy (SST).

[0108] According to certain embodiments, combination regimens of the present invention (e.g., talquetamab, pomalidomide and dexamethasone) improve overall survival (OS) in a population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, wherein the improvement in OS is relative to OS of a reference population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said reference population having been administered either (i) elotuzumab, pomalidomide, and

dexamethasone (EPd) or (ii) pomalidomide, bortezomib, and dexamethasone (PVd). OS refers to time from start of treatment to the date of the subject's death.

Antibodies of the present invention

[0109] Any suitable GPRC5DxCD3 bispecific antibody known to those skilled in the art in view of the present disclosure can be used in the invention.

[0110] Various bispecific antibody formats include formats described herein and recombinant IgG-like dual targeting molecules, wherein the two sides of the molecule each contain the Fab fragment or part of the Fab fragment of at least two different antibodies; IgG fusion molecules, wherein full length IgG antibodies are fused to an extra Fab fragment or parts of Fab fragment; Fc fusion molecules, wherein single chain Fv molecules or stabilized diabodies are fused to heavy-chain constant-domains, Fc-regions or parts thereof; Fab fusion molecules, wherein different Fab-fragments are fused together; ScFv- and diabody-based and heavy chain antibodies (e.g., domain antibodies, nanobodies) wherein different single chain Fv molecules or different diabodies or different heavy-chain antibodies (e.g. domain antibodies, nanobodies) are fused to each other or to another protein or carrier molecule, or bispecific antibodies generated by arm exchange. Exemplary bispecific formats include dual targeting molecules include Dual Targeting (DT)-Ig (GSK/Domantis), Two-in-one Antibody (Genentech) and mAb2 (F-Star), Dual Variable Domain (DVD)-Ig (Abbott), DuoBody (Genmab), Ts2Ab (MedImmune/AZ) and BsAb (Zymogenetics), HERCULES (Biogen Idec) and TvAb (Roche), ScFv/Fc Fusions (Academic Institution), SCORPION (Emergent BioSolutions/Trubion, Zymogenetics/BMS) and Dual Affinity Retargeting Technology (Fc-DART) (MacroGenics), F(ab)2 (Medarex/AMGEN), Dual-Action or Bis-Fab (Genentech), Dock-and-Lock (DNL) (ImmunoMedics), Bivalent Bispecific (Biotecnol) and Fab-Fv (UCB-Celltech), Bispecific T Cell Engager (BITE) (Micromet), Tandem Diabody (Tandab) (Affimed), Dual Affinity Retargeting Technology (DART) (MacroGenics), Single-chain Diabody (Academic), TCR-like Antibodies (AIT, ReceptorLogics), Human Serum Albumin ScFv Fusion (Merrimack) and COMBODY (Epigen Biotech), dual targeting nanobodies (Ablynx), dual targeting heavy chain only domain antibodies. Various formats of bispecific antibodies have been described, for example in Chames and Baty (2009) Curr Opin Drug Disc Dev 12: 276 and in Nunez-Prado et al., (2015) Drug Discovery Today 20(5):588-594.

[0111] In some embodiments, the GPRC5DxCD3 bispecific antibody comprises any one of the GPRC5D binding domains described in U.S. Patent No. 10,562,968, the content of

which is incorporated herein by reference in its entirety. In some embodiments, the GPRC5DxCD3 bispecific antibody comprises any one of the CD3 binding domains described in U.S. Patent No. 10,562,968. In some embodiments, the GPRC5DxCD3 bispecific antibody comprises any one of the GPRC5DxCD3 bispecific antibodies described in U.S. Patent No. 10,562,968.

[0112] In some embodiments, the GPRC5DxCD3 bispecific antibody is chimeric, humanized or human.

[0113] In some embodiments, the bispecific antibody is an IgG1, an IgG2, an IgG3 or an IgG4 isotype. In preferred embodiments, the bispecific antibody is an IgG4 isotype. An exemplary wild-type IgG4 comprises an amino acid sequence of SEQ ID NO: 34.

SEQ ID NO: 34:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCP
APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVH
NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKA
KGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

[0114] The bispecific antibody can be of any allotype. It is expected that allotype has no influence on properties of the bispecific antibodies, such as binding or Fc-mediated effector functions. Immunogenicity of therapeutic antibodies is associated with increased risk of infusion reactions and decreased duration of therapeutic response (Baert et al., (2003) N Engl J Med 348:602-08). The extent to which therapeutic antibodies induce an immune response in the host can be determined in part by the allotype of the antibody (Stickler et al., (2011) Genes and Immunity 12:213-21). Antibody allotype is related to amino acid sequence variations at specific locations in the constant region sequences of the antibody. Table 2 shows select IgG1, IgG2 and IgG4 allotypes.

Table 2.

Allotype	Amino acid residue at position of diversity (residue numbering: EU Index)							
	IgG2		IgG4		IgG1			
	189	282	309	422	214	356	358	431
G2m(n)	T	M						

G2m(n-)	P	V						
G2m(n)/(n-)	T	V						
nG4m(a)			L	R				
G1m(17)					K	E	M	A
G1m(17,1)					K	D	L	A

[0115] In some embodiments, the bispecific antibody comprises one or more Fc substitutions that reduces binding of the bispecific antibody to a Fcγ receptor (FcγR) and/or reduces Fc effector functions such as C1q binding, complement dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) or phagocytosis (ADCP). The specific substitutions can be made in comparison to the wild-type IgG4 of SEQ ID NO: 34.

[0116] Fc positions that can be substituted to reduce binding of the Fc to the activating FcγR and subsequently to reduce effector function are substitutions L234A/L235A on IgG1, V234A/G237A/P238S/H268A/V309L/A330S/P331S on IgG2, F234A/L235A on IgG4, S228P/F234A/ L235A on IgG4, N297A on all Ig isotypes, V234A/G237A on IgG2, K214T/E233P/ L234V/L235A/G236-deleted/A327G/P331A/D365E/L358M on IgG1, H268Q/V309L/ A330S/P331S on IgG2, S267E/L328F on IgG1, L234F/L235E/D265A on IgG1, L234A/L235A/G237A/P238S/H268A/A330S/P331S on IgG1, S228P/F234A/L235A/G237A/P238S on IgG4, and S228P/F234A/L235A/G236-deleted/G237A/P238S on IgG4, wherein residue numbering is according to the EU index.

[0117] Fc substitutions that can be used to reduce CDC are a K322A substitution.

[0118] Well-known S228P substitution can further be made in IgG4 antibodies to enhance IgG4 stability.

[0119] In some embodiments, the bispecific antibody comprises one or more asymmetric substitutions in a first CH3 domain or in a second CH3 domain, or in both the first CH3 domain and the second CH3 domain.

[0120] In some embodiments, the one or more asymmetric substitutions is selected from the group consisting of F405L/K409R, wild-type/F405L_R409K, T366Y/F405A, T366W/F405W, F405W/Y407A, T394W/Y407T, T394S/Y407A, T366W/T394S, F405W/T394S and T366W/T366S_L368A_Y407V, L351Y_F405A_Y407V/T394W, T366I_K392M_T394W/F405A_Y407V, T366L_K392M_T394W/F405A_Y407V, L351Y_Y407A/T366A_K409F, L351Y_Y407A/T366V_K409F, Y407A/T366A_K409F and T350V_L351Y_F405A_Y407V/T350V_T366L_K392L_T394W.

[0121] In some embodiments, the GPRC5DxCD3 bispecific antibody is an IgG4 isotype and comprises phenylalanine at position 405 and arginine at position 409 in a first heavy chain (HC1) and leucine at position 405 and lysine at position 409 in a second heavy chain (HC2), wherein residue numbering is according to the EU Index.

[0122] In some embodiments, the GPRC5DxCD3 bispecific antibody further comprises proline at position 228, alanine at position 234 and alanine at position 235 in both the HC1 and the HC2.

[0123] Tables 3 and 4 provide sequences of an exemplary embodiment of a GPRC5DxCD3 bispecific antibody, according to the Kabat numbering system.

Table 3. Sequences of GPRC5D binding arm

	Region	Sequence	SEQ ID NO:
	HCDR1	GYTMN	4
	HCDR2	LINPYNSDTNYAQKLQG	5
	HCDR3	VALRVALDY	6
	LCDR1	KASQNVATHVG	7
	LCDR2	SASYRYS	8
	LCDR3	QQYNRYPYT	9
	VH	QVQLVQSGAEVKKPGASVKVSCKASGYSF TGYTMNWVRQAPGQGLEWMGLINPYNSD TNYAQKLQGRVTMTTDTSTSTAYMELRSL RSDDTAVYYCARVALRVALDYWGQGTLV TVSS	10
	VL	DIQMTQSPSSLSASVGDRVTITCKASQNVA THVGWYQQKPGKAPKRLIYSASYRYSGVP SRFSGSGSGTEFTLTISNLQPEDFATYYCQQ YNRYPYTFGQGTKLEIK	11
	HC	QVQLVQSGAEVKKPGASVKVSCKASGYSF TGYTMNWVRQAPGQGLEWMGLINPYNSD TNYAQKLQGRVTMTTDTSTSTAYMELRSL RSDDTAVYYCARVALRVALDYWGQGTLV TVSSASTKGPSVFPLAPCSRSTSESTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTPEVTCVVVDV SQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKS LSLSLGK	12

	LC	DIQMTQSPSSLSASVGDRVTITCKASQNVA THVGWYQQKPGKAPKRLIYSASYRYSGVP SRFSGSGSGTEFTLTISNLQPEDFATYYCQQ YNRYPYTFGQGTKLEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC	13

Table 4. Sequences of CD3 binding arm

	Region	Sequence	SEQ ID NO:
	HCDR1	TYAMN	14
	HCDR2	RIRSKYNNYATYYAASVKG	15
	HCDR3	HGNFGNSYVSWFAY	16
	LCDR1	RSSTGAVTTSNYAN	17
	LCDR2	GTNKRAP	18
	LCDR3	ALWYSNLWV	19
	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFNT YAMNWVRQAPGKGLEWVARIRSKYNNYAT YYAASVKGRFTISRDDSKNSLYLQMNSLKTE DTAVYYCARHGNFGNSYVSWFAYWGQGTL VTVSS	20
	VL	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTT SNYANWVQQKPGQAPRGLIGGTNKRAPGTP ARFSGSLLGGKAALTLSGVQPEDEAEYYCAL WYSNLWVFGGGTKLTVLGQP	21
	HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFNT YAMNWVRQAPGKGLEWVARIRSKYNNYAT YYAASVKGRFTISRDDSKNSLYLQMNSLKTE DTAVYYCARHGNFGNSYVSWFAYWGQGTL VTVSSASTKGPSVFPLAPCSRSTSESTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHK PSNTKVDKRVESKYGPPCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPS SIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFLLYSKLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	22
	LC	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTT SNYANWVQQKPGQAPRGLIGGTNKRAPGTP ARFSGSLLGGKAALTLSGVQPEDEAEYYCAL WYSNLWVFGGGTKLTVLGQPKAAPSVTLFP	23

		PSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLT PEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	

[0124] In some embodiments, the GPRC5DxCD3 bispecific antibody is JNJ-64407564 or Talquetamab (also referred to herein as Tal), which has the sequences described in Tables 3 and 4.

[0125] Talquetamab is a GPRC5D-directed bispecific antibody in development for treatment of patients with relapsed or refractory multiple myeloma. *See, e.g.*, Chari A, et al. Blood 2022; 140 (suppl 1): 384-387, which is incorporated by reference herein. Talquetamab is a bispecific GPRC5D-directed CD3 T cell engager in development as a monotherapy for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three or four prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

[0126] Talquetamab and its methods of use are described, for example, in WO 2018/017786 and WO 2022/058445, which are incorporated by reference herein. According to particular embodiments, the GPRC5DxCD3 bispecific antibody has an amino acid sequence with at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% sequence identity to the amino acid sequence of talquetamab.

[0127] Additional embodiments of GPRC5DxCD3 bispecific antibodies that may be used in combination regimens of the present invention are described below.

[0128] In certain embodiments, the GPRC5DxCD3 bispecific antibody comprises a GPRC5D binding domain comprising the HCDR1 of SEQ ID NO: 4, the HCDR2 of SEQ ID NO: 5, the HCDR3 of SEQ ID NO: 6, the LCDR1 of SEQ ID NO: 7, the LCDR2 of SEQ ID NO: 8 and the LCDR3 of SEQ ID NO: 9, and a CD3 binding domain comprising the HCDR1 of SEQ ID NO: 14, the HCDR2 of SEQ ID NO: 15, the HCDR3 of SEQ ID NO: 16, the LCDR1 of SEQ ID NO: 17, the LCDR2 of SEQ ID NO: 18 and the LCDR3 of SEQ ID NO: 19.

[0129] In certain embodiments, the GPRC5D binding domain comprises a heavy chain variable region (VH) having the amino acid sequence of SEQ ID NO: 10 and a light chain variable region (VL) having the amino acid sequence of SEQ ID NO: 11, and the CD3 binding domain comprises a heavy chain variable region (VH) having the amino acid sequence of SEQ ID NO: 20 and a light chain variable region (VL) having the amino acid sequence of SEQ ID NO: 21.

[0130] In certain embodiments, the GPRC5DxCD3 bispecific antibody is an IgG1, an IgG2, an IgG3 or an IgG4 isotype.

[0131] In certain embodiments, the GPRC5DxCD3 bispecific antibody is an IgG4 isotype.

[0132] In certain embodiments, the GPRC5DxCD3 bispecific antibody comprises one or more substitutions in its Fc region.

[0133] In certain embodiments, the GPRC5DxCD3 bispecific antibody is an IgG4 isotype and comprises S228P, F234A and L235A substitutions in its Fc region.

[0134] In certain embodiments, the GPRC5DxCD3 bispecific antibody is an IgG4 isotype and comprises S228P, F234A, L235A F405L and R409K substitutions in its Fc region.

[0135] In certain embodiments, the GPRC5D binding arm comprises S228P, F234A and L235A substitutions in its Fc region (according to EU index numbering).

[0136] In certain embodiments, the Fc region of the CD3 binding arm comprises S228P, F234A, L235A, F405L, and R409K substitutions in its Fc region (according to EU index numbering).

[0137] In certain embodiments, the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having the amino acid sequence of SEQ ID NO: 23.

[0138] In certain embodiments, the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 90% identity to the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having at least 90% identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 90% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 90% identity to the amino acid sequence of SEQ ID NO: 23.

[0139] In certain embodiments, the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 95% identity to the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having at least 95% identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 95% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 95% identity to the amino acid sequence of SEQ ID NO: 23.

[0140] In certain embodiments, the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 98% identity to the amino acid sequence of SEQ ID NO:

12, a first light chain (LC1) having at least 98% identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 98% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 98% identity to the amino acid sequence of SEQ ID NO: 23.

[0141] In certain embodiments, the GPRC5DxCD3 bispecific antibody is talquetamab.

Patient populations with multiple myeloma

[0142] The GPRC5DxCD3 bispecific antibodies disclosed herein are for use in treating multiple myeloma in a subject, for example a human subject. In certain embodiments, the subject is relapsed or refractory to treatment with one or more prior anti-cancer treatments. Relapsed disease means a cancer has come back. Refractory disease means a cancer has not improved with treatment or has stopped responding to treatment.

[0143] In certain embodiments, the subject has relapsed or refractory multiple myeloma and received at least 1 prior line of therapy including a PI and lenalidomide.

[0144] In certain embodiments, the subject has relapsed or refractory multiple myeloma and received 1 to 4 prior lines of therapy including an anti-CD38 antibody and lenalidomide.

[0145] In some embodiments, the subject is relapsed or refractory to treatment with a therapeutic used to treat multiple myeloma or other hematological malignancies.

[0146] In certain embodiments, the subject has had been treated with from 1 to 11 prior lines of therapy, or from 1 to 10 prior lines of therapy.

[0147] In certain embodiments, the subject has previously received an autologous stem cell transplant (ASCT).

[0148] In certain embodiments, the subject has received at least three prior lines of therapy.

[0149] In certain embodiments, the subject has received at least four prior lines of therapy.

[0150] In certain embodiments, the subject has received at least five prior lines of therapy (penta-drug exposed).

[0151] In certain embodiments, the subject has received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

[0152] In certain embodiments, the subject has received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

[0153] In particular embodiments, the patients are relapsed or refractory or intolerant to the last line of therapy (LOT); were exposed to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 therapy; and had measurable disease.

[0154] In some embodiments, the subject has received three anti-cancer therapies prior to administration of the GPRC5DxCD3 bispecific antibody.

[0155] In one embodiment, the three prior anti-cancer therapies are a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody. In certain such embodiments, the proteasome inhibitor is bortezomib, carfilzomib or ixazomib, the immunomodulatory drug (IMiD) is lenalidomide, pomalidomide or thalidomide and the anti-CD38 antibody is daratumumab or isatuximab.

[0156] In one embodiment, the proteasome inhibitor is bortezomib, the immunomodulatory drug (IMiD) is lenalidomide and the anti-CD38 antibody is daratumumab. In one embodiment, the proteasome inhibitor is bortezomib, the immunomodulatory drug (IMiD) is lenalidomide and the anti-CD38 antibody is isatuximab. In one embodiment, the proteasome inhibitor is bortezomib, the immunomodulatory drug (IMiD) is pomalidomide and the anti-CD38 antibody is daratumumab. In one embodiment, the proteasome inhibitor is bortezomib, the immunomodulatory drug (IMiD) is pomalidomide and the anti-CD38 antibody is isatuximab. In one embodiment, the proteasome inhibitor is bortezomib, the immunomodulatory drug (IMiD) is thalidomide and the anti-CD38 antibody is daratumumab. In one embodiment, the proteasome inhibitor is bortezomib, the immunomodulatory drug (IMiD) is thalidomide and the anti-CD38 antibody is isatuximab.

[0157] In one embodiment, the proteasome inhibitor is carfilzomib, the immunomodulatory drug (IMiD) is lenalidomide and the anti-CD38 antibody is daratumumab. In one embodiment, the proteasome inhibitor is carfilzomib, the immunomodulatory drug (IMiD) is lenalidomide and the anti-CD38 antibody is isatuximab. In one embodiment, the proteasome inhibitor is carfilzomib, the immunomodulatory drug (IMiD) is pomalidomide and the anti-CD38 antibody is daratumumab. In one embodiment, the proteasome inhibitor is carfilzomib, the immunomodulatory drug (IMiD) is pomalidomide and the anti-CD38 antibody is isatuximab. In one embodiment, the proteasome inhibitor is carfilzomib, the immunomodulatory drug (IMiD) is thalidomide and the anti-CD38 antibody is daratumumab. In one embodiment, the proteasome inhibitor is carfilzomib, the immunomodulatory drug (IMiD) is thalidomide and the anti-CD38 antibody is isatuximab.

[0158] In one embodiment, the proteasome inhibitor is ixazomib, the immunomodulatory drug (IMiD) is lenalidomide and the anti-CD38 antibody is daratumumab. In one embodiment, the proteasome inhibitor is ixazomib, the immunomodulatory drug (IMiD) is lenalidomide and the anti-CD38 antibody is isatuximab. In one embodiment, the proteasome inhibitor is ixazomib, the immunomodulatory drug (IMiD) is pomalidomide and the anti-CD38 antibody is daratumumab. In one embodiment, the proteasome inhibitor is ixazomib, the immunomodulatory drug (IMiD) is pomalidomide and the anti-CD38 antibody is isatuximab. In one embodiment, the proteasome inhibitor is ixazomib, the immunomodulatory drug (IMiD) is thalidomide and the anti-CD38 antibody is daratumumab. In one embodiment, the proteasome inhibitor is ixazomib, the immunomodulatory drug (IMiD) is thalidomide and the anti-CD38 antibody is isatuximab.

[0159] In some embodiments, the subject is refractory or relapsed to treatment with one or more treatments or therapies, such as THALOMID® (thalidomide), REVLIMID® (lenalidomide), POMALYST® (pomalidomide), VELCADE® (bortezomib), NINLARO (ixazomib), KYPROLIS® (carfilzomib), FARADYK® (panobinostat), AREDIA® (pamidronate), ZOMETA® (zoledronic acid), DARZALEX® (daratumumab), elotozumab or melphalan, Xpovio ® (Selinexor), Venclexta ® (Venetoclax), GSK 916, CAR-T therapies, or other BCMA-directed therapies.

[0160] Various qualitative and/or quantitative methods can be used to determine relapse or refractory nature of the disease. Symptoms that can be associated are for example a decline or plateau of the well-being of the patient or re-establishment or worsening of various symptoms associated with solid tumors, and/or the spread of cancerous cells in the body from one location to other organs, tissues or cells.

[0161] In some embodiments, the multiple myeloma is relapsed or refractory to treatment with an anti-CD38 antibody, selinexor, venetoclax, lenalinomide, bortezomib, pomalidomide, carfilzomib, elotozumab, ixazomib, melphalan or thalidomide, or any combination thereof.

[0162] In one embodiment, the anti-CD38 antibody is daratumumab.

[0163] In another embodiment, the anti-CD38 antibody is isatuximab.

[0164] As described below, in additional embodiments of the present invention, the subject is not relapsed/refractory to prior anti-myeloma treatment, but instead has newly diagnosed multiple myeloma according to IMWG diagnostic criteria and is ineligible or not intended for ASCT as initial therapy.

[0165] In some embodiments, the multiple myeloma is a high-risk multiple myeloma. Subjects with high-risk multiple myeloma are known to relapse early and have poor prognosis and outcome. Subjects can be classified as having high-risk multiple myeloma is they have one or more of the following cytogenetic abnormalities: t(4;14)(p16;q32), t(14;16)(q32;q23), del17p, 1qAmp, t(4;14)(p16;q32) and t(14;16)(q32;q23), t(4;14)(p16;q32) and del17p, t(14;16)(q32;q23) and del17p, or t(4;14)(p16;q32), t(14;16)(q32;q23) and del17p. In some embodiments, the subject having the high-risk multiple myeloma has one or more chromosomal abnormalities comprising: t(4;14)(p16;q32), t(14;16)(q32;q23), del17p, 1qAmp, t(4;14)(p16;q32) and t(14;16)(q32;q23), t(4;14)(p16;q32) and del17p, t(14;16)(q32;q23) and del17p; or t(4;14)(p16;q32), t(14;16)(q32;q23) and del17p, or any combination thereof.

[0166] The cytogenetic abnormalities can be detected for example by fluorescent in situ hybridization (FISH). In chromosomal translocations, an oncogene is translocated to the IgH region on chromosome 14q32, resulting in dysregulation of these genes. t(4;14)(p16;q32) involves translocation of fibroblast growth factor receptor 3 (FGFR3) and multiple myeloma SET domain containing protein (MMSET) (also called WHSC1/NSD2), and t(14;16)(q32;q23) involves translocation of the MAF transcription factor C-MAF. Deletion of 17p (del17p) involves loss of the p53 gene locus.

[0167] Chromosomal rearrangements can be identified using well known methods, for example fluorescent in situ hybridization, karyotyping, pulsed field gel electrophoresis, or sequencing.

Combination regimens comprising a GPRC5DxCD3 bispecific antibody

[0168] The inventors have developed novel combinations regimens comprising GPRC5DxCD3 bispecific antibodies and pomalidomide (pom) that provide deep and durable efficacy.

[0169] As used herein, "weight-based" refers to administration of a dose amount that is based on the subject's specific body weight; for example, 3 mg/kg refers to a dose of 3 milligrams of antibody per kilogram of the subject's body weight. Unless otherwise specified herein, when a dose is described in a unit of "mg/kg" or "μg/kg," weight-based dosing is being employed.

[0170] Unless otherwise specified herein, a GPRC5DxCD3 bispecific antibody, such as talquetamab, is administered on a dosing schedule based on sequential 28-day cycles, for

example, Cycle 1 starts on Day 1 of Cycle 1 and ends on Day 28 of Cycle 1, and then Day 1 of Cycle 2 starts the day after Day 28 of Cycle 1 and ends on Day 28 of Cycle 2, and then Day 1 of Cycle 3 starts the day after Day 28 of Cycle 2 and ends on Day 28 of Cycle 3, and so on. In certain embodiments, one or more step-up doses are administered prior to the first treatment cycle, i.e., prior to Cycle 1 Day 1. Thus, a treatment cycle, as used herein, refers to a 28-day treatment cycle. As used herein with respect to treatment cycles, "C1" refers to Cycle 1, "C2" refers to Cycle 2, "C3" refers to Cycle 3, and so on. Multiple cycles may also be described, e.g., "C3-6" refers to Cycles 3-6 (Cycles 3, 4, 5 and 6). A cycle number with a "+" symbol refers to that cycle and all subsequent cycles, e.g., "C5+" refers to from Cycle 5 and all subsequent cycles (i.e., C5, C6, C7, C8, C9, and so on).

[0171] As used herein "Q4W" means once every four weeks, "Q2W" (also referred to as "bi-weekly" or "biweekly") means once every two weeks, and "QW" (also referred to as "weekly") means once weekly. Q4W may be referred to herein as "monthly" but technically refers to once every 4 weeks or once every 28 days (e.g., in 28-day cycles, a first treatment dose occurs on Day 1 of Cycle 1, a second treatment dose occurs on Day 1 of Cycle 2, etc.). Administration of a treatment dose once weekly (QW) is also referred to herein as a weekly dosing schedule; for example, a 28-day treatment cycle may have a weekly dosing schedule that comprises four doses one week apart from each other (e.g., on Days 1, 8, 15 and 22), or three doses one week apart from each other (e.g., on Days 8, 15 and 22), or two doses one week apart from each other (e.g., on Days 8 and 15). Administration of a treatment dose once every two weeks (Q2W) is also referred to herein as a bi-weekly dosing schedule. Administration of a treatment dose once every four weeks (Q4W) is also referred to herein as a monthly dosing schedule. Dosing regimens may be described herein in terms of the dose amount and frequency; for example, "C1: 0.4 mg/kg QW" refers to administration of 0.4 mg/kg once per week in Cycle 1 of a therapeutically effective regimen, "C3-6: 0.8 mg/kg Q2W" refers to administration of 0.8 mg/kg once every two weeks from Cycle 3 through Cycle 6, "C7+: 0.8 mg/kg Q4W" refers to administration of 0.8 mg/kg once every four weeks starting in Cycle 7, etc.

[0172] As used herein, a "GPRC5DxCD3 treatment cycle" refers to each treatment cycle in a therapeutically effective regimen in which at least one treatment dose of a GPRC5DxCD3 bispecific antibody is administered to the subject. In preferred embodiments, the first GPRC5DxCD3 treatment cycle in a therapeutically effective regimen is preceded by a step-up phase.

[0173] As used herein, a "pomalidomide treatment cycle" refers to each treatment cycle in a therapeutically effective regimen in which at least one treatment dose of pomalidomide is administered to the subject.

[0174] According to embodiments of the present invention, methods of treating multiple myeloma are effective in eliciting a clinical response in a subject as determined by International Myeloma Working Group (IMWG) response criteria. Unless otherwise specified herein, "IMWG criteria" refers to IMWG (2016) criteria. According to particular embodiments, the methods of treatment are effective in eliciting a partial response, a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria. As used herein, overall response rate (ORR) refers to the percentage of patients in a population that achieve a partial response (PR) or better, i.e., a partial response, very good partial response, complete response or stringent complete response. IMWG criteria for response to Multiple Myeloma treatment are provided in Table 7 below.

Table 7

Response	Response Criteria
sCR=stringent complete response	□ CR as defined below, *plus* □ Normal FLC ratio, *and* □ Absence of clonal PCs by immunohistochemistry, immunofluorescence[a] or 2- to 4-color flow cytometry
CR=complete response	□ Negative immunofixation on the serum and urine, *and* □ Disappearance of any soft tissue plasmacytomas, *and* □ <5% PCs in bone marrow
VGPR=very good partial response	□ Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or* □ **≥90% reduction in serum M-protein plus urine M-**protein <100 mg/24 hours
PR=partial response	□ **≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200** mg/24 hours □ If the serum and urine M-protein are not **measurable, a decrease of ≥50% in the difference** between involved and uninvolved FLC levels is required in place of the M-protein criteria □ If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, **≥50% reduction in bone marrow PCs is required in** place of M-protein,

	provided baseline bone marrow plasma cell **percentage was ≥30%** □ In addition to the above criteria, if present at **baseline, a ≥50% reduction in the size of soft tissue** plasmacytomas is also required.

CR=complete response; FLC=free light chain; IMWG=International Myeloma Working Group; M-protein=monoclonal paraprotein; MR=minimal response; PC=plasma cell; PD=progressive disease; PR=partial response; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response

[a] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of >4:1 or <1:2.

* Clarifications to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such subjects requires a >90% decrease in the difference between involved and uninvolved FLC levels.

[0175] IMWG criteria for response to Multiple Myeloma treatment are also described, for example, in Durie et al., Kumar et al. and Rajkumar et al., which are incorporated by reference herein: Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(9):1467-1473; Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-346; Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical Trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-4695.

[0176] In certain embodiments, the GPRC5DxCD3 bispecific antibody (e.g., talquetamab) may be subcutaneously administered according to one or both of the following weight-based dosing schedules (QW and/or Q2W) shown in Tables 9 and 10, wherein mg/kg refers to mg of talquetamab per kg of the patient's body weight:

Table 9

Phase	Day	Talquetamab Dose[a]
Step-up Phase	Day 1	0.01 mg/kg
	Day 3[b]	0.06 mg/kg
	Day 5[b]	0.4 mg/kg
Treatment Phase	Once a week thereafter[c]	0.4 mg/kg

[a] Based on actual body weight.
[b] Dose may be administered between 2 to 4 days after the previous dose and may be given up to 7 days after the previous dose to allow for resolution of adverse reactions.
[c] Maintain a minimum of 6 days between weekly doses and a minimum of 12 days between biweekly (every 2 weeks) doses.

Table 10

Phase	Day	Talquetamab Dose[a]
Step-up Phase	Day 1	0.01 mg/kg
	Day 3[b]	0.06 mg/kg
	Day 5[b]	0.4 mg/kg
	Day 7[b]	0.8 mg/kg
Treatment Phase	Once every 2 weeks thereafter[c]	0.8 mg/kg

[a] Based on actual body weight.
[b] Dose may be administered between 2 to 4 days after the previous dose and may be given up to 7 days after the previous dose to allow for resolution of adverse reactions.
[c] Maintain a minimum of 6 days between weekly doses and a minimum of 12 days between biweekly (every 2 weeks) doses.

[0177] In certain embodiments, the method comprises subcutaneously administering treatment doses of the GPRC5DxCD3 bispecific antibody in an amount of either (i) 0.4 mg/kg weekly (QW), or (ii) 0.8 mg/kg bi-weekly (Q2W).

[0178] In certain embodiments, the method comprises subcutaneously administering treatment doses of the GPRC5DxCD3 bispecific antibody in an amount of 0.8 mg/kg bi-weekly (Q2W).

[0179] In certain embodiments, the method comprises subcutaneously administering treatment doses of the GPRC5DxCD3 bispecific antibody in an amount of 0.8 mg/kg on a bi-weekly (Q2W) dosing schedule, followed by monthly (Q4W) dosing schedule if the subject has achieved a certain clinical response.

[0180] In certain embodiments, the method comprises subcutaneously administering treatment doses of the GPRC5DxCD3 bispecific antibody in an amount of 0.8 mg/kg on a bi-weekly (Q2W) dosing schedule, followed by monthly (Q4W) dosing schedule if the subject has achieved a VGPR or better.

[0181] In certain embodiments, the method comprises subcutaneously administering treatment doses of the GPRC5DxCD3 bispecific antibody in an amount of 0.8 mg/kg on a bi-weekly (Q2W) dosing schedule, followed by monthly (Q4W) dosing schedule if the subject has achieved a PR or better.

[0182] In certain embodiments, the method comprises subcutaneously administering to the subject one or more step-up doses of the GPRC5DxCD3 bispecific antibody prior to administering the first treatment dose of the GPRC5DxCD3 bispecific antibody.

[0183] In certain embodiments, the method comprises subcutaneously administering 2 or 3 step-up doses of the GPRC5DxCD3 bispecific antibody prior to subcutaneously administering the first treatment dose.

[0184] In certain embodiments, the method comprises subcutaneously administering step-up doses of 0.01 mg/kg and 0.06 mg/kg of the GPRC5DxCD3 bispecific antibody prior to subcutaneously administering a treatment dose.

[0185] In certain embodiments, the method comprises subcutaneously administering step-up doses of 0.01 mg/kg, 0.06 mg/kg and 0.4 mg/kg of the GPRC5DxCD3 bispecific antibody prior to subcutaneously administering a treatment dose.

[0186] In certain embodiments, the method comprises subcutaneously administering step-up doses of the GPRC5DxCD3 bispecific antibody 2-4 days apart from each other.

[0187] In certain embodiments, the method comprises orally administering the pomalidomide in an amount of 2 mg daily or 4 mg daily.

[0188] In certain embodiments, the method comprises administering a combination regimen that includes the GPRC5DxCD3 bispecific antibody (e.g., talquetamab), pomalidomide and dexamethasone.

[0189] In certain embodiments, the combination therapy comprises sequential 28-day treatment cycles.

[0190] In certain embodiments, the pomalidomide is administered in an amount of 2 mg daily or 4 mg daily for Days 1-21 of each pomalidomide treatment cycle.

[0191] In certain embodiments, the combination therapy comprises sequential 28-day treatment cycles; administration of the GPRC5DxCD3 bispecific antibody starts in Cycle 1; and administration of the pomalidomide starts in Cycle 2.

[0192] In certain embodiments, the combination therapy comprises sequential 28-day treatment cycles; administration of the GPRC5DxCD3 bispecific antibody starts in Cycle 1; administration of the pomalidomide starts in Cycle 2; and administration of dexamethasone

starts in Cycle 2. In certain embodiments, the dexamethasone is administered during Cycles 2-4 only.

[0193] In certain embodiments, the combination therapy comprises sequential 28-day treatment cycles; Cycle 1 is a step-up phase comprising administration of one or more step-up doses and one or more treatment doses of the GPRC5DxCD3 bispecific antibody; and each subsequent treatment cycle (Cycle 2 onward) comprises oral administration of the pomalidomide in an amount of 2 mg daily on Days 1-21; and subcutaneous administration of the GPRC5DxCD3 bispecific antibody in an amount of either (i) 0.4 mg/kg weekly (QW), or (ii) 0.8 mg/kg bi-weekly (Q2W).

[0194] In certain embodiments, the combination therapy comprises sequential 28-day treatment cycles; Cycle 1 is a step-up phase comprising administration of a first step-up dose of 0.01 mg/kg, a second step-up dose of 0.06 mg/kg, a third step-up dose of 0.4 mg/kg, and a first treatment dose of 0.8 mg/kg of the GPRC5DxCD3 bispecific antibody; and each subsequent treatment cycle (Cycle 2 onward) comprises oral administration of the pomalidomide in an amount of 2 mg daily on Days 1-21; and subcutaneous administration of the GPRC5DxCD3 bispecific antibody in an amount of 0.8 mg/kg bi-weekly (Q2W) (e.g., on Days 1 and 15). In certain embodiments, the GPRC5DxCD3 bispecific antibody is administered bi-weekly (Q2W) during treatment Cycles 2-4 or treatment Cycles 2-6 before switching to a monthly (Q4W) dosing regimen. In certain embodiments, treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a VGPR or better (a very good partial response, a complete response or a stringent complete response), as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, regardless of clinical response in the subject.

[0195] In certain embodiments, the method comprises treating the subject according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein: one or more step-up doses of the GPRC5DxCD3 bispecific antibody (e.g., talquetamab) are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg, wherein the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a

monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, if the subject has achieved a partial response, a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria, and the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, wherein the pomalidomide may optionally be administered in an amount of 4 mg daily (instead of 2 mg daily) on Days 1-21 of each treatment cycle, starting in treatment Cycle 3.

[0196] In certain embodiments, the subject has received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, and the method comprises: treating the subject according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein: one or more step-up doses of the GPRC5DxCD3 bispecific antibody (e.g., talquetamab) are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg, wherein the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, if the subject has achieved a partial response, a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria, and the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, wherein the pomalidomide may optionally be administered in an amount of 4 mg daily (instead of 2 mg daily) on Days 1-21 of each treatment cycle, starting in treatment Cycle 3.

[0197] In certain embodiments, the subject achieves a clinical response that is a partial response, a very good partial response, a complete response, or a stringent complete response.

[0198] In certain embodiments, the GPRC5DxCD3 bispecific antibody (e.g., talquetamab) and pomalidomide are administered according to the dosing schedule illustrated in FIG. 5b.

In certain embodiments, the GPRC5DxCD3 bispecific antibody (e.g., talquetamab), pomalidomide and dexamethasone are administered according to the dosing schedule illustrated in FIG. 5b. In certain embodiments, the GPRC5DxCD3 bispecific antibody (e.g., talquetamab) and pomalidomide are administered according to the dosing schedule illustrated in FIG. 5c. In certain embodiments, the GPRC5DxCD3 bispecific antibody (e.g., talquetamab), pomalidomide and dexamethasone are administered according to the dosing schedule illustrated in FIG. 5c. In certain embodiments, pretreatment medications are administered according to the schedule illustrated in FIG. 5a.

[0199] In certain embodiments, the subject has received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, and the method comprises: treating the subject according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein: one or more step-up doses of the GPRC5DxCD3 bispecific antibody (e.g., talquetamab) are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg, wherein the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, regardless of clinical response in the subject, and the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, wherein the pomalidomide may optionally be administered in an amount of 4 mg daily (instead of 2 mg daily) on Days 1-21 of each treatment cycle, starting in treatment Cycle 3.

[0200] In certain embodiments, the method further comprises administering dexamethasone to the subject. In certain embodiments, the dexamethasone is administered orally or intravenously in an amount of 40 mg (or equivalent). In certain embodiments, the dexamethasone is administered orally or intravenously in an amount of 40 mg (or equivalent) once per week (e.g., on Days 1, 8, 15 and 22) during treatment Cycles 2-4 only.

[0201] In certain embodiments, talquetamab, pomalidomide and dexamethasone are administered as follows, in 28-day treatment cycles:

- In Cycle 1, the following doses of subcutaneous talquetamab are administered:
    - Talquetamab step-up dose 1 (SU1): 0.01 mg/kg, administered on Day 1;
    - Talquetamab step-up dose 2 (SU2): 0.06 mg/kg, administered ≥2d after SU1, between Days 3-6;
    - Talquetamab treatment dose (sometimes referred to as step-up dose 3): 0.4 mg/kg, administered ≥2d after SU2, between Days 5-10;
    - Talquetamab treatment dose: 0.8mg/kg, administered ≥2d after first treatment dose (step-up dose 3) of 0.4 mg/kg, between Days 7-15;
- In subsequent treatment cycles following Cycle 1, the subcutaneous Talquetamab treatment dose of 0.8mg/kg are administered as follows:
    - Cycle 2 – Cycle 4 (C2-C4), Talquetamab SC is administered bi-weekly (Q2W), i.e., 14 days (±3d) after prior treatment dose;
    - From Cycle 5 (C5), if confirmed VGPR or better, schedule can change to Q4W dosing (Day 1 of each 28-day cycle only);
    - Q4W from Cycle 7 (C7) regardless of clinical response;
- Dexamethasone (40 mg or equivalent) is administered weekly (Days 1, 8, 15, and 22) during Cycles 2-4 only (for participants <75 years of age with BMI <18.5 or ≥75 years of age, the weekly dose of dexamethasone is 20 mg); and
- Pomalidomide is administered daily on Days 1-21 of each 28-day cycle, starting in Cycle 2 (≥7d between the course of pomalidomide treatment for each cycle), wherein Pom is initiated at 2 mg daily at Cycle 2 Day 1, and may be increased to 4 mg daily from Cycle 3 Day 1.

[0202] In certain embodiments, talquetamab, pomalidomide and dexamethasone are administered as follows, in 28-day treatment cycles:

- In Cycle 1, the 2 or 3 step-up doses of subcutaneous talquetamab are administered 2-4 days apart from eather other, and then a 0.8 mg/kg treatment dose of subcutaneous talquetamab is administered ≥2 days after the previous dose;
- In subsequent treatment cycles following Cycle 1, the subcutaneous Talquetamab treatment dose of 0.8mg/kg is administered as follows:

- Cycle 2 – Cycle 4 (C2-C4), Talquetamab SC is administered bi-weekly (Q2W);
- From Cycle 5 (C5), if confirmed VGPR or better, schedule can change to Q4W dosing (Day 1 of each 28-day cycle only ±3 days);
- At Cycle 7 Day 1 (±3d), if confirmed PR or better, schedule changes to Q4W dosing; for a subject who is not in confirmed PR or better at C7D1, continue with Q2W dosing until confirmed PR or better is acheived;

- Dexamethasone (40 mg or equivalent) is administered weekly during Cycles 2-4 only (for a subject <75 years of age with BMI <18.5 or ≥75 years of age, the weekly dose of dexamethasone is 20 mg); and
- Pomalidomide is administered daily on Days 1-21 of each 28-day cycle, starting in Cycle 2 (≥7d between the course of pomalidomide treatment for each cycle), wherein Pom is initiated at 2 mg daily at Cycle 2 Day 1, and may be increased to 4 mg daily from Cycle 3 Day 1.

[0203] In certain embodiments, talquetamab, pomalidomide and dexamethasone are administered as follows, in 28-day treatment cycles:

- In Cycle 1, the following doses of subcutaneous talquetamab are administered:
  - Talquetamab step-up dose 1 (SU1): 0.01 mg/kg, administered on Day 1;
  - Talquetamab step-up dose 2 (SU2): 0.06 mg/kg, administered ≥2d after SU1, between Days 3-6;
  - Talquetamab treatment dose (sometimes referred to as step-up dose 3): 0.4 mg/kg, administered ≥2d after SU2, between Days 5-10;
  - Talquetamab treatment dose: 0.8mg/kg, administered ≥2d after first treatment dose (step-up dose 3) of 0.4 mg/kg, between Days 7-15,
- In subsequent treatment cycles following Cycle 1, the subcutaneous Talquetamab treatment dose of 0.8mg/kg is administered as follows:
  - Cycle 2 – Cycle 4 (C2-C4), Talquetamab SC is administered bi-weekly (Q2W), i.e., 14 days (±3d) after prior treatment dose;
  - From Cycle 5 (C5), if confirmed VGPR or better, schedule can change to Q4W dosing (Day 1 of each 28-day cycle only; change to Q4W dosing should occur on C5 or C6 Day 1 ±3d);

- At Cycle 7 Day 1 (±3d), if confirmed PR or better, schedule changes to Q4W dosing; for a subject not in confirmed PR or better at C7D1, continue with Q2W dosing until confirmed PR or better is achieved;
- Dexamethasone (40 mg or equivalent) is administered weekly (Days 1, 8, 15, and 22) during Cycles 2-4 only (for a subject <75 years of age with BMI <18.5 or ≥75 years of age, the weekly dose of dexamethasone is 20 mg); and
- Pomalidomide is administered daily on Days 1-21 of each 28-day cycle, starting in Cycle 2 (≥7d between the course of pomalidomide treatment for each cycle), wherein Pom is initiated at 2 mg daily at Cycle 2 Day 1, and may be increased to 4 mg daily from Cycle 3 Day 1.

[0204] In certain embodiments, a method of improving median progression free survival (PFS) in a population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide comprises administering to the population of subjects a combination therapy comprising a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody (e.g., talquetamab), a therapeutically effective amount of pomalidomide and a therapeutically effective amount of dexamethasone, wherein the method comprises: treating the subject according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein one or more step-up doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg, wherein the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, regardless of clinical response in the subject, and wherein the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, wherein the pomalidomide may optionally be administered in an amount of 4 mg daily (instead of 2 mg daily) on Days 1-21 of each treatment cycle, starting in treatment Cycle 3, and wherein the dexamethasone is administered orally or intravenously

in an amount of 40 mg (or equivalent) once per week (e.g., on Days 1, 8, 15 and 22) during treatment Cycles 2-4 only, wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said reference population having been administered either (i) elotuzumab, pomalidomide, and dexamethasone (EPd) or (ii) pomalidomide, bortezomib, and dexamethasone (PVd).

Combination Regimens Comprising Talquetamab and Daratumumab

[0205] Another embodiment of the present invention provides a method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a combination therapy comprising a GPRC5DxCD3 bispecific antibody described herein (e.g., talquetamab), pomalidomide and daratumumab according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein the subject has relapsed or refractory multiple myeloma and received at least 1 prior line of therapy including a PI and lenalidomide, and wherein:

one or more step-up doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg, and

the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, if the subject has achieved a partial response, a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria, and

the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, and

the daratumumab is subcutaneously administered in an amount of 1800 mg weekly during treatment cycles 1-2, bi-weekly (Q2W) during treatment cycles 3-6: and monthly

(Q4W) during all subsequent treatment cycles 7+. According to certain embodiments, the subject achieves longer PFS compared to a subject that is administered a combination regimen comprising daratumumab, pomalidomide and dexamethasone (DPd) without a GPRC5DxCD3 bispecific antibody.

[0206] Another embodiment of the present invention provides a method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a combination therapy comprising talquetamab, pomalidomide and daratumumab according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein the subject has relapsed or refractory multiple myeloma and received at least 1 prior line of therapy including a PI and lenalidomide, and wherein:

one or more step-up doses of the talquetamab are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the talquetamab is subcutaneously administered to the subject in an amount of 0.8 mg/kg, and

the treatment doses of the talquetamab are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the talquetamab are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, if the subject has achieved a partial response, a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria, and

the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, and

the daratumumab is subcutaneously administered in an amount of 1800 mg weekly during treatment cycles 1-2, bi-weekly (Q2W) during treatment cycles 3-6: and monthly (Q4W) during all subsequent treatment cycles 7+. According to certain embodiments, the subject achieves longer PFS compared to a subject that is administered a combination regimen comprising daratumumab, pomalidomide and dexamethasone (DPd) without talquetamab.

[0207] Another embodiment of the present invention provides a method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a combination therapy comprising a GPRC5DxCD3 bispecific antibody described herein (e.g., talquetamab), pomalidomide and daratumumab according to a therapeutically effective

regimen that comprises sequential 28-day treatment cycles, wherein the subject has relapsed or refractory multiple myeloma and received at least 1 prior line of therapy including a PI and lenalidomide, and wherein:

one or more step-up doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg, and

the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, if the subject has achieved a partial response, a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria, and

the daratumumab is subcutaneously administered in an amount of 1800 mg weekly during treatment cycles 1-2, bi-weekly (Q2W) during treatment cycles 3-6: and monthly (Q4W) during all subsequent treatment cycles 7+. According to certain embodiments, the subject achieves longer PFS compared to a subject that is administered a combination regimen comprising daratumumab, pomalidomide and dexamethasone (DPd) without a GPRC5DxCD3 bispecific antibody.

[0208] Another embodiment of the present invention provides a method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a combination therapy comprising talquetamab and daratumumab according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein the subject has relapsed or refractory multiple myeloma and received at least 1 prior line of therapy including a PI and lenalidomide, and wherein:

one or more step-up doses of the talquetamab are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the talquetamab is subcutaneously administered to the subject in an amount of 0.8 mg/kg, and

the treatment doses of the talquetamab are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and

then treatment doses of the talquetamab are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, if the subject has achieved a partial response, a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria, and

the daratumumab is subcutaneously administered in an amount of 1800 mg weekly during treatment cycles 1-2, bi-weekly (Q2W) during treatment cycles 3-6: and monthly (Q4W) during all subsequent treatment cycles 7+. According to certain embodiments, the subject achieves longer PFS compared to a subject that is administered a combination regimen comprising daratumumab, pomalidomide and dexamethasone (DPd) without talquetamab.

[0209] A non-limiting example of a dosing regimen of the present invention is provided below, in which talquetamab, daratumumab and pomalidomide are administered as a combination regimen in 28-day treatment cycles:

- **Talquetamab subcutaneous (SC) Step-up Dose 1: 10 µg/kg; Step-up Dose 2: 60 µg/kg; Step-up Dose 3: 400 µg/kg; treatment dose 800 µg/kg:**
    - Cycle 1: Step-up Dose 1: Day 2; Step-up Dose 2: Day 4 (+2 days); Step-up Dose 3: Day 8 (+2 days); treatment dose: Day 15 (+2 days)
        - Note: Step-up Dose 2 and Step-up Dose 3 may be administered on Day 3 and Day 7
    - Cycles 2-4: treatment dose on Days 1 and 15
    - Cycles 5-6: Days 1 and 15 or if confirmed VGPR or better, may change to Q4W dosing (Day 1 only)
    - From Cycle 7: Q4W dosing (Day 1 only) for a subject with response of confirmed PR or better. All other subjects continue Q2W dosing (Days 1 and 15) until response of confirmed PR or better is achieved.
- **Daratumumab SC 1800 mg:**
    - Cycles 1-2: Days 1, 8, 15 and 22
    - Cycles 3-6: Days 1 and 15
    - Subsequent cycles: Day 1
- **Pomalidomide (oral) 2 mg:**
    - Cycle 2 and subsequent cycles: Days 1-21

[0210] Another non-limiting example of a dosing regimen of the present invention is provided below, in which talquetamab and daratumumab are administered as a combination regimen in 28-day treatment cycles:

- **Talquetamab subcutaneous (SC) Step-up Dose 1: 10 µg/kg; Step-up Dose 2: 60 µg/kg; Step-up Dose 3: 400 µg/kg; treatment dose 800 µg/kg:**
    - Cycle 1: Step-up Dose 1: Day 2; Step-up Dose 2: Day 4 (+2 days); Step-up Dose 3: Day 8 (+2 days); treatment dose: Day 15 (+2 days)
        - Note: Step-up Dose 2 and Step-up Dose 3 may be administered on Day 3 and Day 7
    - Cycles 2-4: treatment dose on Days 1 and 15
    - Cycles 5-6: Days 1 and 15 or if confirmed VGPR or better, may change to Q4W dosing (Day 1 only)
    - From Cycle 7: Q4W dosing (Day 1 only) for a subject with response of confirmed PR or better. All other subjects continue Q2W dosing (Days 1 and 15) until response of confirmed PR or better is achieved.
- **Daratumumab SC 1800 mg:**
    - Cycles 1-2: Days 1, 8, 15 and 22
    - Cycles 3-6: Days 1 and 15
    - Subsequent cycles: Day 1

Newly Diagnosed Multiple Myeloma

[0211] Embodiments of the present invention also provide novel dosing regimens for the treatment of multiple myeloma in subjects with newly diagnosed multiple myeloma who are either ineligible or not intended for autologous stem cell transplant (ASCT) as initial therapy. Subjects that are newly diagnosed have a diagnosis of multiple myeloma according to the IMWG diagnostic criteria and have not received any prior therapy for multiple myeloma or smoldering myeloma (but may have received a short course of corticosteroids, not exceeding 40 mg of dexamethasone, or equivalent per day for a maximum of 4 days, total of 160 mg dexamethasone or equivalent). Thus, newly diagnosed subjects do not have relapsed/refractory multiple myeloma (RRMM), i.e., they are not relapsed and/or refractory to prior multiple myeloma therapy (but may have received a short course of corticosteroids, not exceeding 40 mg of dexamethasone, or equivalent per day for a maximum of 4 days, total of 160 mg dexamethasone or equivalent).

[0212] Subjects that are ineligible for ASCT as initial therapy can be ineligible due to (i) advanced age, or (ii) presence of comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with ASCT. Subjects that are "not intended" for ASCT as initial therapy are clinically fit enough to undergo ASCT but defer this treatment option.

[0213] According to an embodiment, talquetamab, daratumumab and lenalidomide ("Tal-DR") are administered as a combination therapy for the treatment of adult patients with newly diagnosed multiple myeloma who are either ineligible or not intended for autologous stem cell transplant as initial therapy. According to an embodiment, talquetamab, daratumumab and lenalidomide are administered as a combination therapy for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant as initial therapy.

[0214] According to certain embodiments, Tal-DR improves PFS (progression-free survival) and/or the rate of sustained MRD-negative CR (≥12 months) compared with DRd in subjects with newly diagnosed multiple myeloma who are ineligible or not intended for ASCT as initial therapy.

[0215] According to certain embodiments, talquetamab in combination with daratumumab subcutaneous (SC) and lenalidomide provide an efficacious and safe approach with higher efficacy rates (e.g., mPFS, mOS and MRD negativity rates) compared to the existing standard of care of daratumumab, lenalidomide and dexamethasone (DRd) and/or bortezomib, lenalidomide and dexamethasone (VRd).

[0216] An embodiment of the present invention provides a method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a combination therapy comprising talquetamab, lenalidomide and daratumumab according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein the subject has newly diagnosed multiple myeloma according to IMWG diagnostic criteria and is ineligible or not intended for ASCT as initial therapy, and wherein:

one or more step-up doses of the talquetamab are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the talquetamab is subcutaneously administered to the subject in an amount of 0.8 mg/kg on a monthly dosing schedule (Q4W) starting in treatment cycle 2, and

the lenalidomide is orally administered in an amount of 25 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, and

daratumumab is subcutaneously administered in an amount of 1800 mg weekly during treatment cycles 1-2, bi-weekly (Q2W) during treatment cycles 3-6: and monthly (Q4W) during all subsequent treatment cycles 7+. According to certain embodiments, the method further comprises administering dexamethasone to the subject; for example, the dexamethasone may be administered orally or intravenously in an amount of 20 mg (or equivalent) once per week during treatment Cycles 2 and 3. According to certain embodiments, the subject achieves longer PFS compared to a subject that is administered a combination regimen comprising daratumumab, lenalidomide and dexamethasone (DRd) without talquetamab.

[0217] A non-limiting example of a dosing regimen of the present invention is provided below, in which talquetamab, daratumumab and lenalidomide are administered in 28-day treatment cycles:

Study Treatment	**Dose Schedule (each cycle = 28 days)**
Talquetamab SC	C1: 3 step-up doses (0.01, 0.06, and 0.4 mg/kg) on Days 2, 4, and 8 followed by treatment dose (0.8 mg/kg) on Day 15 C2+: Q4W treatment doses (0.8 mg/kg) on Day 1
Daratumumab SC 1800 mg	C1-2: weekly on Days 1, 8, 15, and 22 C3-6: Q2W on Days 1 and 15 C7+: Q4W on Day 1
Lenalidomide oral 25 mg*	C2+: D1-21
Dexamethasone oral/IV 20 mg**	C2-3: weekly on Days 1, 8, 15, and 22

* Lenalidomide dose may need to be adjusted for participants with reduced CrCl.
** Dexamethasone (16 mg) will be administered as pretreatment medication on Days 1, 2, 4, and 8 of Cycle 1.

Alternative Dosing Regimens Comprising Fewer Step-Up Doses And/Or Prophylactic Tociluzimab

[0218] Embodiments of the present invention also provide alternative step-up dosing regimens for a GPRC5DxCD3 bispecific antibody such as talquetamab. The inventors have developed shortened step-up dosing schedules that result in the same or similar adverse event profiles in patients (e.g., incidence and/or severity of CRS and/or ICANS) compared to patients that receive step-up dosing over a longer period of time. Such alternative step-up dosing regimens are "compressed" (shortened) so the duration of time the patient needs to be actively monitored for adverse events (e.g., CRS and ICANS) is shortened, thereby improving patient experience.

[0219] According to an embodiment, a step-up dosing schedule comprises administering only two step-up doses of a GPRC5DxCD3 bispecific antibody (e.g., talquetamab) before the first treatment dose, wherein the two step-up doses are administered in an amount of 0.03 mg/kg followed by an amount of 0.2 mg/kg. According to another embodiment, a step-up dosing schedule comprises administering only two step-up doses of a GPRC5DxCD3 bispecific antibody (e.g., talquetamab) before the first treatment dose, wherein the two step-up doses are administered in an amount of 0.06 mg/kg followed by an amount of 0.4 mg/kg. According to particular embodiments, the time between the two step-up doses is between about 24 hours and about 72 hours. According to particular embodiments, the first treatment dose is 0.8 mg/kg. According to particular embodiments, the time between the second step-up dose and the first treatment dose is between about 24 hours and about 72 hours.

[0220] According an embodiment, a method of treating multiple myeloma in a subject in need thereof comprises administering to the subject a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody (e.g., talquetamab), wherein the method comprises subcutaneously administering step-up doses on a compressed step-up dosing schedule, wherein the compressed step-up dosing schedule comprises administering only two step-up doses of the GPRC5DxCD3 bispecific antibody before subcutaneously administering a first treatment dose of 0.8 mg/kg, wherein the two step-up doses are administered either (i) in an amount of 0.03 mg/kg followed by an amount of 0.2 mg/kg, or (ii) in an amount of 0.06 mg/kg followed by an amount of 0.4 mg/kg. According to an embodiment, the time between the two step-up doses is between about 24 hours and about 72 hours. According to an embodiment, the time between the second step-up dose and the first treatment dose is between about 24 hours and about 72 hours. According to particular embodiments, the subject is monitored (e.g., by a healthcare professional) for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) while receiving step-up doses, and administration of the compressed step-up dosing schedule shortens the amount of time the subject is monitored for CRS and ICANS. According to particular embodiments, administration of the compressed step-up dosing (e.g., two step-up doses of 0.03 mg/kg and 0.2 mg/kg, or two step-up doses of 0.06 mg/kg and 0.4 mg/kg, with about 24-72 hours between the two step-up doses, and about 24-72 hours between the second step-up dose and first treatment dose) results in no difference, or minimal difference, in incidence and/or severity of CRS exhibited by the subject, compared to a subject that is administered three

step-up doses (e.g., 0.01 mg/kg, 0.06 mg/kg, and 0.4 mg/kg with 2-4 days between the step-up doses and 2-4 days between the third step-up dose and first treatment dose).

[0221] According to an embodiment, the method comprises subcutaneously administering treatment doses of the GPRC5DxCD3 bispecific antibody (preferably talquetamab) in sequential 28-day treatment cycles. In certain embodiments, the method comprises subcutaneously administering the step-up doses during a step-up phase in Cycle 1, and then subcutaneously administering a treatment dose of 0.8 mg/kg every two weeks (Q2W) (e.g., starting from Cycle 1 or Cycle 2). In certain embodiments, the method further comprises subcutaneously administering a treatment dose of 0.8 mg/kg every two weeks (Q2W) and then subcutaneously administering a treatment dose of 0.8 mg/kg every four weeks (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, regardless of clinical response in the subject.

[0222] Embodiments of the present invention also provide methods of reducing the risk of CRS with a GPRC5DxCD3 bispecific antibody (e.g., talquetamab) by administering prophylactic tociluzimab. According to an embodiment, the method comprises administering tocilizumab (e.g., intravenously) to the subject before administering a first step-up dose of the GPRC5DxCD3 bispecific antibody (e.g., talquetamab). According to an embodiment, the tocilizumab is administered in an amount of 8 mg/kg. According to an embodiment, the tocilizumab is administered about 3 hrs before the first step-up dose. tocilizumab. According to an embodiment, dexamethasone is administered (e.g., orally or intravenously) after each step-up dose and after a first treatment dose of the GPRC5DxCD3 bispecific antibody (e.g., talquetamab). According to an embodiment, the dexamethasone is administered in an amount of 8 mg. According to an embodiment, the dexamethasone is administered in an amount of 8 mg daily for two days after each step-up dose and first full treatment dose. According to an embodiment, administration of the tociluzimab results in reduced incidence and/or severity of CRS exhibited by the subject, compared to a subject that is not administered tociluzimab prior to administration of the GPRC5DxCD3 bispecific antibody. According to an embodiment, administration of the tociluzimab and the dexamethasone results in reduced incidence and/or severity of CRS exhibited by the subject, compared to a subject that is not administered tociluzimab and dexamethasone prior to administration of the GPRC5DxCD3 bispecific antibody.

EXEMPLARY EMBODIMENTS

[0223] Provided below are enumerated embodiments of the present invention. These embodiments are illustrative only and do not limit the scope of the present disclosure or of the claims attached hereto.

1. A method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a combination therapy comprising a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody and a therapeutically effective amount of pomalidomide.

2. The method of embodiment 1, wherein the GPRC5DxCD3 bispecific antibody comprises a GPRC5D binding domain comprising the HCDR1 of SEQ ID NO: 4, the HCDR2 of SEQ ID NO: 5, the HCDR3 of SEQ ID NO: 6, the LCDR1 of SEQ ID NO: 7, the LCDR2 of SEQ ID NO: 8 and the LCDR3 of SEQ ID NO: 9, and a CD3 binding domain comprising the HCDR1 of SEQ ID NO: 14, the HCDR2 of SEQ ID NO: 15, the HCDR3 of SEQ ID NO: 16, the LCDR1 of SEQ ID NO: 17, the LCDR2 of SEQ ID NO: 18 and the LCDR3 of SEQ ID NO: 19.

3. The method of embodiment 1 or 2, wherein the GPRC5DxCD3 bispecific antibody comprises a GPRC5D binding domain comprising a heavy chain variable region (VH) having the amino acid sequence of SEQ ID NO: 10 and a light chain variable region (VL) having the amino acid sequence of SEQ ID NO: 11, and the CD3 binding domain comprises a heavy chain variable region (VH) having the amino acid sequence of SEQ ID NO: 20 and a light chain variable region (VL) having the amino acid sequence of SEQ ID NO: 21.

4. The method of any of embodiments 1-3, wherein the GPRC5DxCD3 bispecific antibody is an IgG1, an IgG2, an IgG3 or an IgG4 isotype.

5. The method of any of embodiments 1-4, wherein the GPRC5DxCD3 bispecific antibody is an IgG4 isotype.

6. The method of any of embodiments 1-5, wherein the GPRC5DxCD3 bispecific antibody comprises one or more substitutions in its Fc region.

7. The method of any of embodiments 1-6, wherein the GPRC5DxCD3 bispecific antibody is an IgG4 isotype and comprises S228P, F234A and L235A substitutions in its Fc region (according to EU numbering).

8. The method of any of embodiments 1-7, wherein the GPRC5DxCD3 bispecific antibody is an IgG4 isotype and comprises S228P, F234A, L235A F405L and R409K substitutions in its Fc region (according to EU numbering).

9. The method of any of embodiments 1-8, wherein the Fc region of the GPRC5D binding arm comprises S228P, F234A and L235A substitutions in its Fc region (according to EU numbering).

10. The method of any of embodiments 1-9, wherein the Fc region of the CD3 binding arm comprises S228P, F234A, L235A, F405L, and R409K substitutions in its Fc region (according to EU numbering).

11. The method of any of embodiments 1-10, wherein the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having the amino acid sequence of SEQ ID NO: 23.

12. The method of any of embodiments 1-10, wherein the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 90% identity to the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having at least 90% identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 90% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 90% identity to the amino acid sequence of SEQ ID NO: 23.

13. The method of any of embodiments 1-10, wherein the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 95% identity to the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having at least 95% identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 95% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 95% identity to the amino acid sequence of SEQ ID NO: 23.

14. The method of any of embodiments 1-10, wherein the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 98% identity to the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having at least 98% identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 98% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 98% identity to the amino acid sequence of SEQ ID NO: 23.

15. The method of any of embodiments 1-10, wherein the GPRC5DxCD3 bispecific antibody is talquetamab.

16. The method of any of embodiments 1-15, wherein the subject has relapsed or refractory multiple myeloma myeloma.

17. The method of any of embodiments 1-16, wherein the subject has received at least two prior lines of therapy.

18. The method of any of embodiments 1-16, wherein the subject has received at least three prior lines of therapy.

19. The method of any of embodiments 1-16, wherein the subject has received at least four prior lines of therapy, and/or the subject is penta-drug exposed.

20. The method of any of embodiments 1-16, wherein the subject has received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

21. The method of any of embodiments 1-16, wherein the subject has received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

22. The method of any of embodiments 1-21 comprising subcutaneously administering treatment doses of the GPRC5DxCD3 bispecific antibody in an amount of either (i) 0.4 mg/kg weekly (QW), or (ii) 0.8 mg/kg bi-weekly (Q2W).

23. The method of any of embodiments 1-21 comprising subcutaneously administering treatment doses of the GPRC5DxCD3 bispecific antibody in an amount of 0.4 mg/kg weekly (QW).

24. The method of any of embodiments 1-21 comprising subcutaneously administering treatment doses of the GPRC5DxCD3 bispecific antibody in an amount of 0.8 mg/kg bi-weekly (Q2W).

25. The method of any of embodiments 1-24 comprising subcutaneously administering to the subject one or more step-up doses of the GPRC5DxCD3 bispecific antibody prior to administering the first treatment dose of the GPRC5DxCD3 bispecific antibody.

26. The method of any of embodiments 1-25, comprising subcutaneously administering 2 or 3 step-up doses of the GPRC5DxCD3 bispecific antibody prior to subcutaneously administering the first treatment dose.

27. The method of any of embodiments 1-26, comprising (i) subcutaneously administering step-up doses of 0.01 mg/kg and 0.06 mg/kg of the GPRC5DxCD3 bispecific antibody prior to subcutaneously administering a treatment dose, or (ii) subcutaneously administering step-up doses of 0.03 mg/kg and 0.2 mg/kg of the GPRC5DxCD3 bispecific antibody prior to subcutaneously administering a treatment dose, or (iii) subcutaneously administering step-up doses of 0.06 mg/kg and 0.4 mg/kg of the GPRC5DxCD3 bispecific antibody prior to subcutaneously administering a treatment dose.

28. The method of any of embodiments 1-27, comprising subcutaneously administering step-up doses of 0.01 mg/kg, 0.06 mg/kg and 0.4 mg/kg of the GPRC5DxCD3 bispecific antibody prior to subcutaneously administering a treatment dose.

29. The method of any of embodiments 1-28, comprising subcutaneously administering step-up doses of the GPRC5DxCD3 bispecific antibody 2-4 days apart from each other.

30. The method of any of embodiments 1-29 comprising orally administering the pomalidomide in an amount of 2 mg daily or 4 mg daily.

31. The method of any of embodiments 1-29 comprising orally administering the pomalidomide in an amount of 2 mg daily.

32. The method of any of embodiments 1-29 comprising orally administering the pomalidomide in an amount of 4 mg daily.

33. The method of any of embodiments 1-32, wherein the combination therapy comprises sequential 28-day treatment cycles.

34. The method of any of embodiments 1-32, wherein the pomalidomide is administered in an amount of 2 mg daily or 4 mg daily for Days 1-21 of each pomalidomide treatment cycle.

35. The method of any of embodiments 1-32, wherein the pomalidomide is administered in an amount of 2 mg daily for Days 1-21 of each pomalidomide treatment cycle.

36. The method of any of embodiments 1-32, wherein the pomalidomide is administered in an amount of 4 mg daily for Days 1-21 of each pomalidomide treatment cycle.

37. The method of any of embodiments 1-36, wherein:

the combination therapy comprises sequential 28-day treatment cycles;

administration of the GPRC5DxCD3 bispecific antibody starts in Cycle 1; and

administration of the pomalidomide starts in Cycle 2.

38. The method of any of embodiments 1-37, wherein:

the combination therapy comprises sequential 28-day treatment cycles;

Cycle 1 is a step-up phase comprising administration of one or more step-up doses and one or more treatment doses of the GPRC5DxCD3 bispecific antibody; and

each subsequent treatment cycle (Cycle 2 onward) comprises oral administration of the pomalidomide in an amount of 2 mg daily on Days 1-21; and subcutaneous administration of the GPRC5DxCD3 bispecific antibody in an amount of either (i) 0.4 mg/kg weekly (QW), or (ii) 0.8 mg/kg bi-weekly (Q2W).

39. The method of any of embodiments 1-38, wherein:

the combination therapy comprises sequential 28-day treatment cycles;

Cycle 1 is a step-up phase comprising (i) administration of a first step-up dose of 0.01 mg/kg, a second step-up dose of 0.06 mg/kg, a third step-up dose of 0.4 mg/kg, and a first treatment dose of 0.8 mg/kg of the GPRC5DxCD3 bispecific antibody, or (ii) administration of a first step-up dose of 0.03 mg/kg, a second step-up dose of 0.2 mg/kg, and a first treatment dose of 0.8 mg/kg of the GPRC5DxCD3 bispecific antibody, or (iii) administration of a first step-up dose of 0.06 mg/kg, a second step-up dose of 0.4 mg/kg, and a first treatment dose of 0.8 mg/kg of the GPRC5DxCD3 bispecific antibody; and

each subsequent treatment cycle (Cycle 2 onward) comprises oral administration of the pomalidomide in an amount of 2 mg daily on Days 1-21; and subcutaneous administration of the GPRC5DxCD3 bispecific antibody in an amount of 0.8 mg/kg bi-weekly (Q2W) (e.g., on Days 1 and 15).

40. The method of any of embodiments 1-39, wherein the subject achieves a clinical response that is a PR, or a VGPR, or a CR or a sCR.

41. The method of any of embodiments 1-39, wherein the subject achieves a clinical response that is a VGPR, a CR or a sCR.

42. The method of any of embodiments 1-39, wherein the subject achieves a clinical response that is a CR or a sCR.

43. The method of any of embodiments 1-42, wherein the subject has received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, and wherein the method comprises:

treating the subject according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein:

one or more step-up doses of the GPRC5DxCD3 bispecific antibody (e.g., talquetamab) are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg,

wherein the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, regardless of clinical response in the subject, and

the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, wherein the pomalidomide may optionally be administered in an amount of 4 mg daily (instead of 2 mg daily) on Days 1-21 of each treatment cycle, starting in treatment Cycle 3.

44. The method of any of embodiments 1-43, wherein the method further comprises administering dexamethasone to the subject.

45. The method of embodiment 44, wherein the dexamethasone is administered orally or intravenously in an amount of 40 mg (or equivalent) once per wek.

46. The method of embodiment 43, wherein dexamethasone is administered to the subject orally or intravenously in an amount of 40 mg (or equivalent) once per week (e.g., on Days 1, 8, 15 and 22) during treatment Cycles 2-4 only.

47. A method of improving median progression free survival (PFS) in a population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said method comprising administering to the population of subjects a combination therapy comprising a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody (e.g., talquetamab), a therapeutically effective amount of pomalidomide and a therapeutically effective amount of dexamethasone, wherein the method comprises:

treating the subject according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein:

one or more step-up doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg,

wherein the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, regardless of clinical response in the subject, and

wherein the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, wherein the pomalidomide may optionally be administered in an amount of 4 mg daily (instead of 2 mg daily) on Days 1-21 of each treatment cycle, starting in treatment Cycle 3, and

wherein the dexamethasone is administered orally or intravenously in an amount of 40 mg (or equivalent) once per week (e.g., on Days 1, 8, 15 and 22) during treatment Cycles 2-4 only,

wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said reference population having been administered either (i) elotuzumab, pomalidomide, and dexamethasone (EPd) or (ii) pomalidomide, bortezomib, and dexamethasone (PVd).

48. A method of improving overall response rate (ORR) in a population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said method comprising administering to the population of subjects a combination therapy comprising a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody (e.g., talquetamab), a therapeutically effective amount of

pomalidomide and a therapeutically effective amount of dexamethasone, wherein the method comprises:

treating the subject according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein:

one or more step-up doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg,

wherein the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, regardless of clinical response in the subject, and

wherein the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, wherein the pomalidomide may optionally be administered in an amount of 4 mg daily (instead of 2 mg daily) on Days 1-21 of each treatment cycle, starting in treatment Cycle 3, and

wherein the dexamethasone is administered orally or intravenously in an amount of 40 mg (or equivalent) once per week (e.g., on Days 1, 8, 15 and 22) during treatment Cycles 2-4 only,

wherein the improvement in ORR is relative to ORR of a reference population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said reference population having been administered either (i) elotuzumab, pomalidomide, and dexamethasone (EPd) or (ii) pomalidomide, bortezomib, and dexamethasone (PVd).

49. The method of any of embodiments 43-48, wherein the step-up phase comprises (i) subcutaneously administering step-up doses of 0.01 mg/kg and 0.06 mg/kg of the GPRC5DxCD3 bispecific antibody 2-4 days apart from each other (e.g., on Days 1

and 4, respectively), or (ii) subcutaneously administering step-up doses of 0.03 mg/kg and 0.2 mg/kg of the GPRC5DxCD3 bispecific antibody 24-72 hours apart from each other, or (iii) subcutaneously administering step-up doses of 0.06 mg/kg and 0.4 mg/kg of the GPRC5DxCD3 bispecific antibody 24-72 hours apart from each other.

50. The method of any of embodiments 43-48, wherein the step-up phase comprises (i) subcutaneously administering step-up doses of 0.01 mg/kg, 0.06 mg/kg and 0.4 mg/kg of the GPRC5DxCD3 bispecific antibody 2-4 days apart from each other (e.g., on Days 1, 4 and 8, respectively), or (ii) subcutaneously administering step-up doses of 0.03 mg/kg and 0.2 mg/kg of the GPRC5DxCD3 bispecific antibody 24-72 hours apart from each other, or (iii) subcutaneously administering step-up doses of 0.06 mg/kg and 0.4 mg/kg of the GPRC5DxCD3 bispecific antibody 24-72 hours apart from each other.

51. The method of any of embodiments 43-48, wherein the step-up phase comprises (i) subcutaneously administering step-up doses of 0.01 mg/kg, 0.06 mg/kg and 0.4 mg/kg of the GPRC5DxCD3 bispecific antibody 2-4 days apart from each other (e.g., on Days 1, 4 and 8, respectively), or (ii) subcutaneously administering step-up doses of 0.03 mg/kg and 0.2 mg/kg of the GPRC5DxCD3 bispecific antibody 24-72 hours apart from each other, or (iii) subcutaneously administering step-up doses of 0.06 mg/kg and 0.4 mg/kg of the GPRC5DxCD3 bispecific antibody 24-72 hours apart from each other, and then subcutaneously administering the treatment dose of 0.8 mg/kg of the GPRC5DxCD3 bispecific antibody at least two days after the last step-up dose (e.g., between Days 7-15, such as Day 15).

53. The method of any of embodiments 1-42 comprising:

treating the subject according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein:

one or more step-up doses of the GPRC5DxCD3 bispecific antibody (e.g., talquetamab) are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg,

wherein the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has

achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, if the subject has achieved a partial response, a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria, and

the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, wherein the pomalidomide may optionally be administered in an amount of 4 mg daily (instead of 2 mg daily) on Days 1-21 of each treatment cycle, starting in treatment Cycle 3.

54. The method of any of embodiments 1-42, wherein the subject has received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, and wherein the method comprises:

treating the subject according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein:

one or more step-up doses of the GPRC5DxCD3 bispecific antibody (e.g., talquetamab) are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg,

wherein the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, if the subject has achieved a partial response, a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria, and

the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, wherein the pomalidomide may optionally be administered in an amount of 4 mg daily (instead of 2 mg daily) on Days 1-21 of each treatment cycle, starting in treatment Cycle 3.

55. The method of embodiment 53 or 54, wherein the method further comprises administering dexamethasone to the subject.

56. The method of embodiment 55, wherein the dexamethasone is administered orally or intravenously in an amount of 40 mg (or equivalent) once per wek.

57. The method of embodiment 55, wherein the dexamethasone is administered to the subject orally or intravenously in an amount of 40 mg (or equivalent) once per week (e.g., on Days 1, 8, 15 and 22) during treatment Cycles 2-4 only.

58. A method of improving median progression free survival (PFS) in a population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said method comprising administering to the population of subjects a combination therapy comprising a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody (e.g., talquetamab), a therapeutically effective amount of pomalidomide and a therapeutically effective amount of dexamethasone, wherein the method comprises:

treating the subject according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein:

one or more step-up doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg,

wherein the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, if the subject has achieved a partial response, a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria, and

wherein the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, wherein the pomalidomide may optionally be administered in an amount of 4 mg daily (instead of 2 mg daily) on Days 1-21 of each treatment cycle, starting in treatment Cycle 3, and

wherein the dexamethasone is administered orally or intravenously in an amount of 40 mg (or equivalent) once per week (e.g., on Days 1, 8, 15 and 22) during treatment Cycles 2-4 only,

wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said reference population having been administered either (i) elotuzumab, pomalidomide, and dexamethasone (EPd) or (ii) pomalidomide, bortezomib, and dexamethasone (PVd).

59. A method of improving overall response rate (ORR) in a population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said method comprising administering to the population of subjects a combination therapy comprising a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody (e.g., talquetamab), a therapeutically effective amount of pomalidomide and a therapeutically effective amount of dexamethasone, wherein the method comprises:

treating the subject according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein:

one or more step-up doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg,

wherein the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, if the subject has achieved a partial response, a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria, and

wherein the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, wherein the pomalidomide may optionally be administered in an amount of 4 mg daily (instead of 2 mg daily) on Days 1-21 of each treatment cycle, starting in treatment Cycle 3, and

wherein the dexamethasone is administered orally or intravenously in an amount of 40 mg (or equivalent) once per week (e.g., on Days 1, 8, 15 and 22) during treatment Cycles 2-4 only,

wherein the improvement in ORR is relative to ORR of a reference population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said reference population having been administered either (i) elotuzumab, pomalidomide, and dexamethasone (EPd) or (ii) pomalidomide, bortezomib, and dexamethasone (PVd).

60. A method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a combination therapy comprising talquetamab, pomalidomide and daratumumab according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein the subject has relapsed or refractory multiple myeloma and received at least 1 prior line of therapy including a PI and lenalidomide, and wherein:

one or more step-up doses of the talquetamab are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the talquetamab is subcutaneously administered to the subject in an amount of 0.8 mg/kg, and

the treatment doses of the talquetamab are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the talquetamab are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, if the subject has achieved a partial response, a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria, and

the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, and

the daratumumab is subcutaneously administered in an amount of 1800 mg weekly during treatment cycles 1-2, bi-weekly (Q2W) during treatment cycles 3-6: and monthly (Q4W) during all subsequent treatment cycles 7+.

61. A method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a combination therapy comprising talquetamab and daratumumab according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein the subject has relapsed or refractory multiple myeloma and received at least 1 prior line of therapy including a PI and lenalidomide, and wherein:

one or more step-up doses of the talquetamab are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the talquetamab is subcutaneously administered to the subject in an amount of 0.8 mg/kg, and

the treatment doses of the talquetamab are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the talquetamab are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, if the subject has achieved a partial response, a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria, and

the daratumumab is subcutaneously administered in an amount of 1800 mg weekly during treatment cycles 1-2, bi-weekly (Q2W) during treatment cycles 3-6: and monthly (Q4W) during all subsequent treatment cycles 7+.

62. A method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a combination therapy comprising talquetamab, lenalidomide and daratumumab according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein the subject has newly diagnosed multiple myeloma according to IMWG diagnostic criteria and is ineligible or not intended for ASCT as initial therapy, and wherein:

one or more step-up doses of the talquetamab are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the

talquetamab is subcutaneously administered to the subject in an amount of 0.8 mg/kg on a monthly dosing schedule (Q4W) starting in treatment cycle 2, and

the lenalidomide is orally administered in an amount of 25 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, and

daratumumab is subcutaneously administered in an amount of 1800 mg weekly during treatment cycles 1-2, bi-weekly (Q2W) during treatment cycles 3-6: and monthly (Q4W) during all subsequent treatment cycles (7+).

63. The method of embodiment 62, wherein the method further comprises administering dexamethasone to the subject.

64. The method of embodiment 63, wherein the dexamethasone is administered to the subject orally or intravenously in an amount of 20 mg (or equivalent) once per week during treatment Cycles 2 and 3 only.

65. The method of embodiment 60 or 61, wherein the subject achieves longer PFS compared to a subject that is administered a combination regimen comprising daratumumab, pomalidomide and dexamethasone (DPd) without talquetamab.

66. The method of any of embodiments 62-64, wherein the subject achieves longer PFS compared to a subject that is administered a combination regimen comprising daratumumab, lenalidomide and dexamethasone (DRd) without talquetamab.

67. The method of any of embodiments 60-66, wherein the step-up phase comprises subcutaneously administering two or three step-up doses of the talquetamab, e.g., 2-4 days apart from each other or 24-72 hours apart from each other.

68. The method of any of embodiments 60-66, wherein the step-up phase comprises (i) subcutaneously administering step-up doses of 0.01 mg/kg, 0.06 mg/kg and 0.4 mg/kg of the talquetamab 2-4 days apart from each other, or (ii) subcutaneously administering step-up doses of 0.03 mg/kg and 0.2 mg/kg of the talquetamab 24-72 hours apart from each other, or (iii) subcutaneously administering step-up doses of 0.06 mg/kg and 0.4 mg/kg of the talquetamab 24-72 hours apart from each other.

69. The method of embodiment 67 or 68, wherein the step-up phase comprises subcutaneously administering a treatment dose of 0.8 mg/kg after the step-up doses.

70. The method of any of embodiments 1-69 comprising administering only two step-up doses of the GPRC5DxCD3 bispecific antibody (e.g., talquetamab), before the first treatment dose, wherein the two step-up doses are administered in an amount of 0.03 mg/kg followed by an amount of 0.2 mg/kg.

71. The method of any of embodiments 1-69 comprising administering only two step-up doses of the GPRC5DxCD3 bispecific antibody (e.g., talquetamab), before the first treatment dose, wherein the two step-up doses are administered in an amount of 0.06 mg/kg followed by an amount of 0.4 mg/kg.

72. The method of embodiment 70 or 71, wherein the time between the two step-up doses is between about 24 hours and about 72 hours.

73. The method of embodiment 70 or 71, wherein the time between the two step-up doses is between about 2 days and about 4 days.

74. The method of any of embodiments 70-73, wherein the first treatment dose is 0.8 mg/kg.

75. The method of any of embodiments 70-73, wherein the first treatment dose is 0.4 mg/kg.

76. The method of embodiment 74 or 75, wherein the time between the second step-up dose and the first treatment dose is between about 24 hours and about 72 hours.

77. The method of embodiment 74 or 75, wherein the time between the second step-up dose and the first treatment dose is between about 2 days and about 4 days.

78. A method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody (e.g., talquetamab), wherein the method comprises subcutaneously administering step-up doses on a compressed step-up dosing schedule, wherein the compressed step-up dosing schedule comprises administering only two step-up doses of the GPRC5DxCD3 bispecific antibody before subcutaneously administering a first treatment dose of 0.8 mg/kg, wherein the two step-up doses are administered either (i) in an amount of 0.03 mg/kg followed by an amount of 0.2 mg/kg, or (ii) in an amount of 0.06 mg/kg followed by an amount of 0.4 mg/kg.

79. The method of embodiment 78, wherein the two step-up doses are administered in an amount of 0.03 mg/kg followed by an amount of 0.2 mg/kg.

80. The method of embodiment 78, wherein the two step-up doses are administered in an amount of 0.06 mg/kg followed by an amount of 0.4 mg/kg.

81. The method of any of embodiments 78-80, wherein the time between the two step-up doses is between about 24 hours and about 72 hours.

82. The method of any of embodiments 78-80, wherein the time between the two step-up doses is between about 2 days and about 4 days.

83. The method of any of embodiments 78-82, wherein the time between the second step-up dose and the first treatment dose is between about 24 hours and about 72 hours.

84. The method of any of embodiments 78-82, wherein the time between the second step-up dose and the first treatment dose is between about 2 days and about 4 days.

85. The method of any of embodiments 78-84, wherein the method comprises subcutaneously administering treatment doses in sequential 28-day treatment cycles.

86. The method of embodiment 85, wherein the method further comprises subcutaneously administering the step-up doses during a step-up phase in Cycle 1, and subcutaneously administering a treatment dose of 0.8 mg/kg every two weeks (Q2W) (e.g., starting from Cycle 1 or Cycle 2).

87. The method of embodiment 86, wherein the method further comprises subcutaneously administering a treatment dose of 0.8 mg/kg every two weeks (Q2W) and then subcutaneously administering a treatment dose of 0.8 mg/kg every four weeks (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, regardless of clinical response in the subject.

88. The method of any of embodiments 78-87, wherein the GPRC5DxCD3 bispecific antibody comprises a GPRC5D binding domain comprising the HCDR1 of SEQ ID NO: 4, the HCDR2 of SEQ ID NO: 5, the HCDR3 of SEQ ID NO: 6, the LCDR1 of SEQ ID NO: 7, the LCDR2 of SEQ ID NO: 8 and the LCDR3 of SEQ ID NO: 9, and a CD3 binding domain comprising the HCDR1 of SEQ ID NO: 14, the HCDR2 of SEQ ID NO: 15, the HCDR3 of SEQ ID NO: 16, the LCDR1 of SEQ ID NO: 17, the LCDR2 of SEQ ID NO: 18 and the LCDR3 of SEQ ID NO: 19.

89. The method of embodiment 78-88, wherein the GPRC5DxCD3 bispecific antibody comprises a GPRC5D binding domain comprising a heavy chain variable region (VH) having the amino acid sequence of SEQ ID NO: 10 and a light chain variable region (VL) having the amino acid sequence of SEQ ID NO: 11, and the CD3 binding domain comprises a heavy chain variable region (VH) having the amino acid sequence of SEQ ID NO: 20 and a light chain variable region (VL) having the amino acid sequence of SEQ ID NO: 21.

90. The method of any of embodiments 78-89, wherein the GPRC5DxCD3 bispecific antibody is an IgG1, an IgG2, an IgG3 or an IgG4 isotype.

91. The method of any of embodiments 78-90, wherein the GPRC5DxCD3 bispecific antibody is an IgG4 isotype.

92. The method of any of embodiments 78-91, wherein the GPRC5DxCD3 bispecific antibody comprises one or more substitutions in its Fc region.

93. The method of any of embodiments 78-92, wherein the GPRC5DxCD3 bispecific antibody is an IgG4 isotype and comprises S228P, F234A and L235A substitutions in its Fc region (according to EU numbering).

94. The method of any of embodiments 78-93, wherein the GPRC5DxCD3 bispecific antibody is an IgG4 isotype and comprises S228P, F234A, L235A F405L and R409K substitutions in its Fc region (according to EU numbering).

95. The method of any of embodiments 78-94, wherein the Fc region of the GPRC5D binding arm comprises S228P, F234A and L235A substitutions in its Fc region (according to EU numbering).

96. The method of any of embodiments 78-95, wherein the Fc region of the CD3 binding arm comprises S228P, F234A, L235A, F405L, and R409K substitutions in its Fc region (according to EU numbering).

97. The method of any of embodiments 78-96, wherein the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having the amino acid sequence of SEQ ID NO: 23.

98. The method of any of embodiments 78-96, wherein the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 90% identity to the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having at least 90% identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 90% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 90% identity to the amino acid sequence of SEQ ID NO: 23.

99. The method of any of embodiments 78-96, wherein the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 95% identity to the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having at least 95%

identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 95% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 95% identity to the amino acid sequence of SEQ ID NO: 23.

100. The method of any of embodiments 78-96, wherein the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 98% identity to the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having at least 98% identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 98% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 98% identity to the amino acid sequence of SEQ ID NO: 23.

101. The method of any of embodiments 78-97, wherein the GPRC5DxCD3 bispecific antibody is talquetamab.

102. The method of any of embodiments 78-101, wherein the subject has relapsed or refractory multiple myeloma.

103. The method of any of embodiments 78-102, wherein the subject has received at least one prior line or therapy, or at least two prior lines of therapy.

104. The method of any of embodiments 78-102, wherein the subject has received at least three prior lines of therapy.

105. The method of any of embodiments 78-102, wherein the subject has received at least four prior lines of therapy, and/or the subject is penta-drug exposed.

106. The method of any of embodiments 78-102, wherein the subject has received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

107. The method of any of embodiments 78-102, wherein the subject has received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

108. The method of any of embodiments 78-101, wherein the subject has newly diagnosed multiple myeloma according to IMWG diagnostic criteria and is ineligible or not intended for ASCT as initial therapy

109. The method of any of embodiments 78-101, wherein the subject has relapsed or refractory multiple myeloma and received at least 1 prior line of therapy including a PI and lenalidomide.

110. The method of any of embodiments 78-101, wherein the subject has relapsed or refractory multiple myeloma and received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide.

111. The method of any of embodiments 70-110, wherein the subject is monitored (e.g., by a healthcare professional) for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) while receiving step-up doses.

112. The method of embodiment 111, wherein administration of two step-up doses instead of three step-up doses shortens the amount of time the subject is monitored for CRS and ICANS.

113. The method of embodiment 111 or 112, wherein administration of two step-up doses results in no difference, or minimal difference, in incidence and/or severity of CRS exhibited by the subject, compared to a subject that is administered three step-up doses.

114. The method of any of embodiments 1-110, wherein administration of compressed step-up dosing results in no difference, or negligible difference, in incidence and/or severity of CRS exhibited by the subject, compared to a subject that is administered three step-up doses,

wherein said compressed step-up dosing comprises administration of two step-up doses of either (i) 0.03 mg/kg and 0.2 mg/kg, or (ii) 0.06 mg/kg and 0.4 mg/kg, with about 24-72 hours between the two step-up doses, and about 24-72 hours between the second step-up dose and first treatment dose, and

wherein said three step-up doses comprise administration of 0.01 mg/kg, 0.06 mg/kg, and 0.4 mg/kg with 2-4 days between the step-up doses and 2-4 days between the third step-up dose and first treatment dose.

115. The method of any of embodiments 1-114, further comprising administering tocilizumab (e.g., intravenously) to the subject before administering a first step-up dose of the GPRC5DxCD3 bispecific antibody (e.g., talquetamab).

116. The method of embodiment 115, comprising administering the tocilizumab in an amount of 8 mg/kg.

117. The method of embodiment 115 or 116, comprising administering the tocilizumab about 3 hrs before the first step-up dose.

118. The method of any of embodiments 115-117, further comprising administering a glucocorticoid, an antihistamine, and an antipyretic.

119. The method of any of embodiments 1-118, further comprising administering dexamethasone (e.g., orally or intravenously) after each step-up dose and after a first treatment dose of the GPRC5DxCD3 bispecific antibody (e.g., talquetamab).

120. The method of embodiment 119, comprising administering the dexamethasone in an amount of 8 mg.

121. The method of embodiment 119 or 120, comprising administering the dexamethasone in an amount of 8 mg daily for two days after each step-up dose and first full treatment dose.

122. The method of any of embodiments 115-118, wherein administration of the tociluzimab results in reduced incidence and/or severity of CRS exhibited by the subject, compared to a subject that is not administered tociluzimab prior to administration of the GPRC5DxCD3 bispecific antibody.

123. The method of any of embodiments 115-121, wherein administration of the tociluzimab and the dexamethasone results in reduced incidence and/or severity of CRS exhibited by the subject, compared to a subject that is not administered tociluzimab and dexamethasone prior to administration of the GPRC5DxCD3 bispecific antibody.

[0224] Those skilled in the art will appreciate that numerous changes and modifications can be made to the preferred embodiments of the invention and that such changes and modifications can be made without departing from the spirit of the invention. It is, therefore, intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

[0225] The disclosures of each patent, patent application, and publication cited or described in this document are hereby incorporated herein by reference, in its entirety.

EXAMPLES

[0226] The following examples are provided to further describe some of the embodiments disclosed herein. The examples are intended to illustrate, not to limit, the disclosed embodiments.

Example 1: Talquetamab + Pomalidomide in Patients with Relapsed/Refractory Multiple Myeloma: Safety and Preliminary Efficacy Results from the Phase 1b MonumenTAL-2 Study

[0227] Antibodies

[0228] Anti-GPRC5D/anti-CD3 antibody talquetamab (also called Tal) was made by Janssen Pharmaceuticals. Talquetamab comprises a GPRC5D binding arm and a CD3 binding arm, the amino acid sequences of which are shown in Table 5 and Table 6, respectively.

Table 5. Sequences of GPRC5D binding arm

	Region	Sequence	SEQ ID NO:
GPRC5D binding arm	HCDR1	GYTMN	4
	HCDR2	LINPYNSDTNYAQKLQG	5
	HCDR3	VALRVALDY	6
	LCDR1	KASQNVATHVG	7
	LCDR2	SASYRYS	8
	LCDR3	QQYNRYPYT	9
	VH	QVQLVQSGAEVKKPGASVKVSCKASGYSF TGYTMNWVRQAPGQGLEWMGLINPYNSD TNYAQKLQGRVTMTTDTSTSTAYMELRSL RSDDTAVYYCARVALRVALDYWGQGTLV TVSS	10
	VL	DIQMTQSPSSLSASVGDRVTITCKASQNVA THVGWYQQKPGKAPKRLIYSASYRYSGVP SRFSGSGSGTEFTLTISNLQPEDFATYYCQQ YNRYPYTFGQGTKLEIK	11
	HC	QVQLVQSGAEVKKPGASVKVSCKASGYSF TGYTMNWVRQAPGQGLEWMGLINPYNSD TNYAQKLQGRVTMTTDTSTSTAYMELRSL RSDDTAVYYCARVALRVALDYWGQGTLV TVSSASTKGPSVFPLAPCSRSTSESTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTKTYTCNVD HKPSNTKVDKRVESKYGPPCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTPEVTCVVVDV SQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKS LSLSLGK	12
	LC	DIQMTQSPSSLSASVGDRVTITCKASQNVA THVGWYQQKPGKAPKRLIYSASYRYSGVP SRFSGSGSGTEFTLTISNLQPEDFATYYCQQ YNRYPYTFGQGTKLEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDSTYSLSSTL	13

		TLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC	

Table 6. Sequences of CD3 binding arm

	Region	Sequence	SEQ ID NO:
CD3 binding arm	HCDR1	TYAMN	14
	HCDR2	RIRSKYNNYATYYAASVKG	15
	HCDR3	HGNFGNSYVSWFAY	16
	LCDR1	RSSTGAVTTSNYAN	17
	LCDR2	GTNKRAP	18
	LCDR3	ALWYSNLWV	19
	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFNT YAMNWVRQAPGKGLEWVARIRSKYNNYAT YYAASVKGRFTISRDDSKNSLYLQMNSLKTE DTAVYYCARHGNFGNSYVSWFAYWGQGTL VTVSS	20
	VL	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTT SNYANWVQQKPGQAPRGLIGGTNKRAPGTP ARFSGSLLGGKAALTLSGVQPEDEAEYYCAL WYSNLWVFGGGTKLTVLGQP	21
	HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFNT YAMNWVRQAPGKGLEWVARIRSKYNNYAT YYAASVKGRFTISRDDSKNSLYLQMNSLKTE DTAVYYCARHGNFGNSYVSWFAYWGQGTL VTVSSASTKGPSVFPLAPCSRSTSESTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHK PSNTKVDKRVESKYGPPCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPS SIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFLLYSKLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	22
	LC	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTT SNYANWVQQKPGQAPRGLIGGTNKRAPGTP ARFSGSLLGGKAALTLSGVQPEDEAEYYCAL WYSNLWVFGGGTKLTVLGQPKAAPSVTLFP PSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLT PEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	23

[0229] Background

[0230] Talquetamab (tal) is a T-cell redirecting bispecific antibody (BsAb) targeting GPRC5D and CD3. GPRC5D is a novel antigen that is highly expressed on malignant plasma cells but has low expression on B cells and normal plasma cells. Tal has demonstrated deep and durable responses, including in high-risk populations, and a clinically manageable safety profile in patients (pts) with relapsed/refractory multiple myeloma (RRMM) in the MonumenTAL-1 study (NCT03399799/NCT04634552). Pomalidomide (pom) is an immunomodulatory drug (IMiD) that has direct on-tumor apoptotic activity and enhances immune activity. This example reports initial efficacy and safety results of tal + pom from the MonumenTAL-2 study. The tal + pom results represent the first clinical results from a combination therapy comprising a GPRC5D-targeted therapy and an IMiD.

[0231] Methods

[0232] MonumenTAL-2 (NCT05050097) is a multi-arm, phase 1b study of tal in combination with antimyeloma agents in pts with MM. A schematic summary of the MonumenTAL-2 study design is provided in FIG. 1.

[0233] A summary of the patient characteristics of the Tal + Pom cohort of MonumenTAL-2 is provided in FIG. 2. Pts received the recommended phase 2 doses of subcutaneous tal 0.4 mg/kg weekly (QW) or 0.8 mg/kg every other week (Q2W), with step-up dosing, + oral pom 2 mg daily (dose escalation to 4 mg daily permitted) starting in cycle 2. **Pts received ≥2 prior lines of therapy (LOT) including a proteasome inhibitor and an IMiD;** prior T-cell redirection therapies including BsAbs and chimeric antigen receptor (CAR)-T along with prior pom exposure were permitted. CRS and ICANS were graded by ASTCT criteria; all other adverse events (AEs) were graded by CTCAE v5.0. Response was assessed by IMWG criteria. Efficacy endpoints are presented as individual cohorts (QW and Q2W); safety is presented across both cohorts.

[0234] Results (Initial Data Cut-Off)

[0235] As of an initial data cut-off, 35 patients were enrolled with a median follow-up of 11.4 months (range, 1.2–14.9) in the QW cohort (N=16) and 7.7 months (range, 1.6–10.8) in the Q2W cohort (N=19). Median ages were 69.5 years (range, 49–78) and 63.0 years (range, 43–76), respectively; 41.7% and 33.3% of pts had high-risk cytogenetics (del[17p], t[4;14], or t[14;16]) and 12.5% and 10.5% of pts had extramedullary disease, respectively. Median prior LOT were 3 in both cohorts; 25.0% and 21.1% were triple-class refractory, respectively,

and 6.3% were penta-drug refractory (all in QW cohort). Prior treatments included CAR-T (18.8% and 0%), BsAb (6.3% and 0% [0% refractory]), and anti-CD38 Ab (75.0% and 73.7% [56.3% and 36.8% refractory]) in the QW and Q2W cohorts, respectively; 31.3% and 15.8% **had prior pom exposure (18.8% and 5.3% refractory). All pts had ≥1 AE; most common were dysgeusia (77.1%), CRS (74.3%; most grade 1/2, 2.9% grade ≥3), and neutropenia (60.0%).** Grade 3/4 AEs occurred in 88.6% of pts; most common were neutropenia (48.6%), anemia (25.7%), and thrombocytopenia (20.0%). Nail, skin, and rash toxicities occurred in 65.7%, 40.0%, and 20.0% of pts (majority grade 1/2 with no discontinuations), respectively. ICANS occurred in 2 pts (both grade 1). Infections occurred in 71.4% of pts (22.9% grade 3/4); most common were pneumonia (20.0%) and COVID-19 (14.3%). AEs led to dose reduction or schedule change of tal in 34.3% of pts and dose reduction of pom in 31.4% of pts. Two pts (5.7%) in the Q2W cohort had AEs, myocardial infarction and pulmonary embolism (PE), that led to treatment discontinuation (not drug related). One death due to PE occurred (same pt who discontinued treatment). ORR was 86.7% and 83.3% in the QW and Q2W cohorts, **respectively, with ≥CR in 60.0% and 44.4% and ≥VGPR in 86.7% and 77.8%, respectively.** ORRs were consistent across pt subgroups (>80% independent of prior pom or CAR-T exposure). Median time to first response was 1.0 month (range, 0.9–2.1) in the QW cohort and 1.3 months (range, 0–4.8) in the Q2W cohort. At 6 months, 100% of responders were still responding in both cohorts. Median DOR and PFS were not reached, with 6-month PFS rates of 93.3% (QW) and 88.9% (Q2W).

[0236] Additional Results (Subsequent Data Cut-Off)

[0237] As of a later data cut-off (Oct. 2023), ORRs were consistent across patient subgroups and responses deepened over time:

- 100% (3/3) in CAR-T–exposed patients in the QW cohort (no patients had CAR-T exposure in Q2W);
- 100% in (5/5 in QW, 3/3 in Q2W) pomalidomide-exposed patients in both cohorts;
- 50% (1/2 in QW) and 67% (2/3 in Q2W) in patients with EMD; and
- 80% (4/5 in QW) and 75% (3/4 in Q2W) in patients with high-risk cytogenetics.

[0238] A summary of the above results is provided in FIG. 3.

[0239] Responses also deepened over the time, as summarized in the following table:

	Tal 0.4 mg/kg QW + pom	**Tal 0.8 mg/kg Q2W + pom**
Median PFS, months (95% CI)	NR (14.09–NR)	NR (7.43–NR)
9-month PFS rate, % (95% CI)	93.8 (63.2–99.1)	75.5 (46.4–90.3)
Median DOR, months (95% CI)	NR (12.0–NR)	NR (7.4–NR)
9-month DOR rate, % (95% CI)	100.0 (100.0–100.0)	83.9 (49.4–95.7)

[0240] Subsequent Data Cutoff:

[0241] Safety:

[0242] As of a later data cutoff (April 22, 2024), the most common AEs were taste-related events, infections, and CRS. Cytopenias were mostly grade 3/4 and generally limited to the first few cycles. ICANS occurred in 3 pts; all were grade 1. Taste-, skin-, nail-, and rash-related GPRC5D AEs were mainly grade 1/2, with few discontinuations. Nine pts had AEs that led to treatment discontinuation. AEs led to dose reduction of tal or pom in 37.1% and 48.6% of pts, respectively; 65.7% and 77.1% of pts skipped doses of tal and pom due to AEs, respectively. The most common AEs that led to dose reduction of pom included neutropenia, peripheral neuropathy, and fatigue. Dose reductions and schedule changes were used to manage AEs. In pts with and without oral toxicities, weight loss was evident early but stabilized and improved over time; a more gradual trend of improvement was noted in pts with oral toxicities. The most common infections were pneumonia, upper respiratory tract infections, and COVID-19; infections were mainly grade ½. First-onset infections generally occurred in the first few cycles of treatment. Consistent with target expression, there was no reduction in total CD19+
B cells during treatment.

[0243] Efficacy:

[0244] As of the April 22, 2024, data cutoff, ORR was 93.8% (QW) and 84.2% (Q2W) (FIG. 7); additional efficacy outcomes are presented in the following table:

	Tal 0.4 mg/kg QW + pom (n=16)	**Tal 0.8 mg/kg Q2W + pom (n=19)**
Median follow-up, months (range)	20.6 (1.2–25.1)	14.9 (1.2–21.2)
Median time to first response, months (range)	1.2 (0.9–3.3)	1.0 (0–2.6)
Median DOR, months (95% CI)	NR (16.0–NE)	14.3 (8.6–NE)
12-month DOR rate, % (95% CI)	93.3 (61.3–99.0)	52.2 (22.7–75.3)
Median PFS, months (95% CI)	NR (18.1–NE)	12.9 (7.0–NE)
12-month PFS rate, % (95% CI)	87.5 (58.6–96.7)	57.8(31.0–77.4)

[0245] Robust responses were observed in subgroups, including high-risk cytogenetics (75.0–80.0% across cohorts) and prior CAR-T (100% in QW; no pts had CAR-T exposure in Q2W) or pom (100% across cohorts). Although numbers are small, a trend for longer DOR with deeper response is observed, as shown in the following table:

12-month DOR rate, %	**Tal 0.4 mg/kg QW + pom**	**Tal 0.8 mg/kg Q2W + pom**
PR	0.0 (NE–NE) n=1	0.0 (NE–NE) n=1
VGPR	100.0 (100.0–100.0) n=6	50.0 (5.8–84.5) n=5
CR	100.0 (100.0–100.0) n=8	58.3 (18.0–84.4) n=9

[0246] Responses in both cohorts deepened over time.

[0247] **Conclusions:**

[0248] In this first reported combination of a GPRC5D-targeted therapy and an IMiD, tal + pom showed rapid, deep responses in pts with RRMM and ≥2 prior LOT. Specifically, the doublet of talquetamab + pomalidomide showed rapid and deep responses in 93.8% (QW) and 84.2% (Q2W) in patients with RRMM who had ≥2 prior lines of therapy. All 3 patients with prior CAR-T therapy responded. There were ORRs of 100% in patients with prior pomalidomide exposure across cohorts. There were ORRs of ≥50% in EMD and ≥75% in patients with high-risk cytogenetics across cohorts.

[0249] The safety profile of the combination, including grade 3/4 hematologic toxicity, was consistent with the individual agents, with no evidence of additive hematologic toxicities. The majority of nail-, oral-, skin-, and rash-related AEs were grade 1/2 with no

discontinuations. Reduction in CD19+ B cells might explain the relatively low rate of grade 3/4 infections, and further supports the combination as a B-cell preserving regimen.

Example 2: A Study Comparing Talquetamab Plus Pomalidomide, Talquetamab Plus Teclistamab, and Elotuzumab, Pomalidomide, and Dexamethasone or Pomalidomide, Bortezomib, and Dexamethasone in Participants with Relapsed or Refractory Myeloma who Have Received an Anti-CD38 Antibody and Lenalidomide (MonumenTAL-6)

[0250] This is a randomized, Phase 3, active-controlled, parallel, multicenter, interventional, open-label study in participants with relapsed or refractory multiple myeloma who have received 1 to 4 prior lines of therapy including an anti-CD38 mAb and lenalidomide.

[0251] Objectives

[0252] This is a Phase 3 Randomized Study Comparing Talquetamab in Combination with Pomalidomide (Tal-P), Talquetamab in Combination with Teclistamab (Tal-Tec), and Investigator's Choice of Either Elotuzumab, Pomalidomide, and Dexamethasone (EPd) or Pomalidomide, Bortezomib, and Dexamethasone (PVd) in Participants with Relapsed or Refractory Myeloma who Have Received 1 to 4 Prior Lines of Therapy Including an Anti-CD38 Antibody and Lenalidomide.

[0253] The primary objective of this study is to compare the effectiveness of either talquetamab plus pomalidomide (Tal-P) or talquetamab plus teclistamab (Tal-Tec) with elotuzumab, pomalidomide, and dexamethasone (EPd) or pomalidomide, bortezomib, and dexamethasone (PVd). Secondary objectives include to further compare the efficacy of either Tal-P or Tal-Tec with EPd or PVd and to assess the safety and tolerability of Tal-P and Tal-Tec. The primary hypothesis is that Tal-P or Tal-Tec will improve PFS compared with EPd or PVd in participants with relapsed or refractory multiple myeloma who have received 1 to 4 prior lines of therapy including an anti-CD38 mAb and lenalidomide.

[0254] A target of approximately 795 participants randomized in a 1:1:1 ratio to receive Tal-P (ArmA), Tal-Tec (ArmB), or EPd or PVd (ArmC), with stratification by number of **prior lines of therapy (1 versus ≥2), ISS stage at screening (I versus II/III), and investigator's** intended choice of therapy (EPd versus PVd).

[0255] Study Arms and Duration

[0256] Study treatment will be administered in 28-day cycles for Tal-P (Arm A), Tal-Tec (Arm B), and EPd (Arm C). For PVd (Arm C), study treatment will be administered in 21-

day cycles. At the time of screening, based on the investigator's choice, they must declare whether the participant will be treated with EPd or PVd should they be randomized to Arm C.

[0257] Arm A (Tal-Pom) Dosing Schedules

[0258] Dosing schedules for Arm A [Tal-P] are presented in FIG. 5. FIG 5a provides the pretreatment medication schedule and FIG. 5b provides the initial study treatment schedule, which was later updated to the study treatment schedule shown in FIG. 5c.

[0259] Talquetamab: INITIAL Arm A dosing schedule, which was later updated:

[0260] In Cycle 1 (28-day cycle) of Arm A, the following doses of subcutaneous talquetamab will be administered:

- Talquetamab step-up dose 1 (SU1): 0.01 mg/kg, administered on Day 1;
- Talquetamab step-up dose 2 (SU2): 0.06 mg/kg, administered ≥2d after SU1, between Days 3-6;
- Talquetamab treatment dose (sometimes referred to as step-up dose 3): 0.4 mg/kg, administered ≥2d after SU2, between Days 5-10;
- Talquetamab treatment dose: 0.8mg/kg, administered ≥2d after first treatment dose (step-up dose 3) of 0.4 mg/kg, between Days 7-15.

[0261] In subsequent treatment cycles following Cycle 1 (28-day treatment cycles), the subcutaneous Talquetamab treatment dose of 0.8mg/kg will be administered as follows in Arm A:

- Cycle 2 – Cycle 4 (C2-C4), Talquetamab SC is administered bi-weekly (Q2W), i.e., 14 days (±3d) after prior treatment dose;
- From Cycle 5 (C5), if confirmed VGPR or better, schedule can change to Q4W dosing (Day 1 of each 28-day cycle only) per investigator discretion;
- Q4W from Cycle 7 (C7) for all participants.

[0262] Talquetamab: UPDATED Arm A dosing schedule:

[0263] In Cycle 1 (28-day cycle) of Arm A, the following doses of subcutaneous talquetamab will be administered:

- Talquetamab step-up dose 1 (SU1): 0.01 mg/kg, administered on Day 1;
- Talquetamab step-up dose 2 (SU2): 0.06 mg/kg, administered ≥2d after SU1, between Days 3-6;
- Talquetamab treatment dose (sometimes referred to as step-up dose 3): 0.4 mg/kg, administered ≥2d after SU2, between Days 5-10;

- Talquetamab treatment dose: 0.8mg/kg, administered ≥2d after first treatment dose (step-up dose 3) of 0.4 mg/kg, between Days 7-15.

[0264] In subsequent treatment cycles following Cycle 1 (28-day treatment cycles), the subcutaneous Talquetamab treatment dose of 0.8mg/kg will be administered as follows in Arm A:

- Cycle 2 – Cycle 4 (C2-C4), Talquetamab SC is administered bi-weekly (Q2W), i.e., 14 days (±3d) after prior treatment dose;
- From Cycle 5 (C5), if confirmed VGPR or better, schedule can change to Q4W dosing (Day 1 of each 28-day cycle only) per investigator discretion (change to Q4W dosing should occur on C5 or C6 Day 1 ±3d);
- At Cycle 7 Day 1 (±3d), participants with response of confirmed PR or better must change to Q4W dosing. In exceptional cases only, participants can continue Q2W dosing after sponsor consultation and approval. For all participants who are not in confirmed PR or better at C7D1, continue with Q2W dosing until confirmed PR or better is achieved.

[0265] **Dexamethasone: Arm A dosing schedule**

[0266] Dexamethasone (40 mg or equivalent) will be administered weekly (Days 1, 8, 15, and 22) during Cycles 2-4 only. For participants <75 years of age with BMI <18.5 or ≥75 years of age, the weekly dose of dexamethasone is 20 mg.

[0267] **Pomalidomide: Arm A dosing schedule**

[0268] Pomalidomide will be administered daily on Days 1-21 of each 28-day cycle, starting in Cycle 2 (≥7d between the course of pomalidomide treatment for each cycle). Pom will be initiated at 2 mg daily at Cycle 2 Day 1, and may be increased to 4 mg daily per investigator discretion from Cycle 3 Day 1. The selected dose regimen for pomalidomide is based on standard doses used in clinical practice for the treatment of multiple myeloma, as detailed in respective product information. Participants can continue therapy with pomalidomide beyond Cycle 26 if no discontinuation criteria are met.

[0269] **Arm B (Tal-Tec) Dosing Schedule**

[0270] In Arm B, participants will receive therapy with Tal/Tec for up to 26 cycles if they have no sign of progressive disease or toxicity. An initial Arm B dosing schedule was later updated in a protocol amendment, as a result of developing data from other clinical studies involving Tal and Tec. For example, the RedirecTT-1 study's exploratory E-R analysis demonstrated a trend for improved depth of response associated with Q2W talquetamab

dosing in the initial treatment cycles. A reduction in talquetamab dose frequency after response does not compromise efficacy and may ameliorate GPRC5D specific AEs.

[0271] Talquetamab Arm B dosing schedule:

[0272] Talquetamab will be administered as follows, in 28-day treatment cycles:

- In Cycle 1, the following doses of subcutaneous talquetamab are administered:
  - Talquetamab step-up dose 1 (SU1): 0.01 mg/kg, administered on Day 1;
  - Talquetamab step-up dose 2 (SU2): 0.06 mg/kg, administered ≥2d after SU1;
  - Talquetamab treatment dose (sometimes referred to as step-up dose 3): 0.4 mg/kg, administered ≥2d after SU2;
  - Talquetamab treatment dose: 0.8 mg/kg, administered ≥2d after first treatment dose (step-up dose 3) of 0.4 mg/kg, between Days 7-15;
- In subsequent treatment cycles following Cycle 1, the subcutaneous Talquetamab treatment doses of 0.8mg/kg are administered as follows:
  - Cycle 2 – Cycle 4 (C2-C4), Talquetamab SC is administered bi-weekly (Q2W), i.e., 14 days (±3d) after prior treatment dose;
  - From Cycle 5 (C5), if confirmed VGPR or better, schedule can change to Q4W dosing (Day 1 of each 28-day cycle only), with the change to Q4W occurring on Cycle 5 or Cycle 6 Day 1 (±3d);
  - At Cycle 7 Day 1 (±3d), if confirmed PR or better, schedule must change to Q4W dosing;
  - At Cycle 7 Day 1 (±3d), if not in confirmed PR or better, continue with Q2W dosing until confirmed PR or better is achieved.

[0273] Teclistamab Arm B dosing schedule:

[0274] Teclistamab will be administered as follows, in 28-day treatment cycles:

- In Cycle 1, the following doses of subcutaneous teclistamab are administered:
  - Tec step-up dose 1 (SU1): 0.06 mg/kg, administered on Day 1;
  - Tec step-up dose 2 (SU2): 0.3 mg/kg, administered ≥2d after SU1;
  - Tec treatment dose (sometimes referred to as step-up dose 3): 1.5 mg/kg, administered ≥2d after SU2;

- Tec treatment dose: 1.5 mg/kg, administered ≥2d after first treatment dose (step-up dose 3) of 1.5 mg/kg, between Days 7-15.

- In subsequent treatment cycles following Cycle 1, the subcutaneous Tec treatment doses of 3.0 mg/kg are administered as follows:
  - From Cycle 2 (C2), Q4W dosing (Day 1 only) for all participants (regardless of clinical response).

[0275] When talquetamab SC and teclistamab SC are to be administered on the same day, the two drugs are to be given at least 15 minutes apart (it is suggested to administer talquetamab first).

[0276] **Arm C (EPd or PVd) Dosing Schedules**

[0277] The pretreatment medication schedule for participants receiving EPd is provided in FIG 6a. The study treatment schedule for participants receiving EPd is provided in FIG 6b. The study treatment schedule for participants receiving PVd is provided in FIG 6c.

[0278] **Efficacy Evaluations**

[0279] Efficacy assessments will occur per IMWG criteria (2016) as defined in the protocol using data from serum, urine, bone marrow, and imaging (if applicable). Responses or progression will be evaluated by investigators, use of a computerized algorithm, and by an IRC; assessment by the IRC will be used as the primary analysis.

[0280] **Primary Outcome Measures:**

- Progression Free Survival (PFS) [Time Frame: Up to 7 years 2 months]

PFS is defined as the duration from the date of randomization to either progressive disease or death, whichever comes first.

[0281] **Secondary Outcome Measures:**

- Overall Response Rate (ORR) [Time Frame: Up to 7 years 2 months]

ORR is defined as the percentage of participants with best overall response of partial response (PR) or better according to international myeloma working group (IMWG) response criteria.

- Complete Response (CR) or Better Rate [Time Frame: Up to 7 years 2 months]

CR or better is defined as the percentage of participants with best overall response of CR or better according to IMWG response criteria.

- Very Good Partial Response (VGPR) or Better Rate [Time Frame: Up to 7 years 2 months]

VGPR or better is defined as the percentage of participants with best overall response of VGPR or better rate according to IMWG response criteria.

- Minimal Residual Disease (MRD)-negative CR Rate [Time Frame: Up to 7 years 2 months]

MRD-negative CR is defined as the percentage of participants who achieve both CR or better and MRD negativity at a threshold of 10^-5 at any timepoint after the date of randomization and before disease progression or start of subsequent antimyeloma therapy (SST).

- Overall Survival (OS) [Time Frame: Up to 7 years 2 months]

OS is defined as the time from randomization to the date of participant's death.

- Progression Free Survival on Next-line Therapy (PFS2) [Time Frame: Up to 7 years 2 months]

PFS2 is defined as time from randomization to progression on the next line of therapy or death, whichever comes first.

- Time to Next Treatment (TTNT) [Time Frame: Up to 7 years 2 months]

TTNT is defined as the time from randomization to the start of SST.

- Serum Concentration of Talquetamab and Teclistamab [Time Frame: Up to 7 years 2 months]

Serum concentration of talquetamab and teclistamab will be reported.

- Number of Participants with Anti-drug Antibodies (ADAs) to Talquetamab and Teclistamab [Time Frame: Up to 7 years 2 months]

Number of participants with ADAs to talquetamab and teclistamab will be reported.

- Time to Sustained Worsening in Symptoms, Functioning, and Health-related Quality of Life (HRQoL) as Assessed by Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q) [Time Frame: Up to 7 years 2 months]

Time to sustained worsening in symptoms, functioning and HRQoL is defined as the interval from the date of randomization to the start date of meaningful change. The MySIm-Q is a disease-specific patient-reported outcome (PRO) assessment complementary to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item (EORTC-QLQ-C30). It includes 17 items resulting in a symptom subscale and an impact subscale.

- Time to Sustained Worsening in Symptoms, Functioning, and Health-related Quality of Life (HRQoL) as Assessed by EORTC-QLQ-C30 [Time Frame: Up to 7 years 2 months]

Time to sustained worsening in symptoms, functioning and HRQoL is defined as the interval from the date of randomization to the start date of meaningful change. EORTC-QLQ-C30 Version 3 includes 30 items that make up 5 functional scales (physical, role, emotional, cognitive, and social), 1 global health status scale, 3 symptom scales (pain, fatigue, and nausea or vomiting), and 5 single symptom items (dyspnea, insomnia, appetite loss, constipation, and diarrhea) and a single impact item (financial difficulties). The recall period is 7 days ("past week"), and responses are reported using a verbal and numeric rating scales. The item and scale scores are transformed to a 0 to 100 scale. A high scale score represents a higher response level.

- Time to Sustained Worsening in Symptoms, Functioning, and Health-related Quality of Life (HRQoL) as Assessed by EuroQol Five Dimension Questionnaire 5-Level (EQ-5D-5L) [Time Frame: Up to 7 years 2 months]

Time to sustained worsening in symptoms, functioning and HRQoL is defined as the interval from the date of randomization to the start date of meaningful change. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain or discomfort, and anxiety or depression plus a visual analog scale rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

- Time to Sustained Worsening in Symptoms, Functioning, and Health-related Quality of Life (HRQoL) as Assessed by Patient Global Impression –Severity (PGI-S) [Time Frame: Up to 7 years 2 months]

Time to sustained worsening in symptoms, functioning and HRQoL is defined as the interval from the date of randomization to the start date of meaningful change. The PGI-S will be used as an anchor, external criterion, to determine meaningful change in scores for the MySIm-Q and EORTC-QLQ-C30 in this population. The response options are presented as a 5-point verbal rating scale from “none” to “very severe.”

- Time to Sustained Worsening in Symptoms, Functioning, and Health-related Quality of Life (HRQoL) as Assessed by Epstein Taste Survey [Time Frame: Up to 7 years 2 months]

Time to sustained worsening in symptoms, functioning and HRQoL is defined as the interval from the date of randomization to the start date of meaningful change. The epstein taste

survey consists of 17 items from the full 71 item PRO instrument, specific to taste changes. developed for use in patients with head and neck cancer as a composite of the Vanderbilt Head and Neck Symptom Survey.

- Change from Baseline in Symptoms, Functioning, and Health-related Quality of Life (HRQoL) as Assessed by MySIm-Q [Time Frame: Up to 7 years 2 months]

Change from baseline in symptoms, functioning, and HRQoL as assessed by MySIm-Q will be reported. The MySIm-Q is a disease-specific patient-reported outcome (PRO) assessment complementary to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item (EORTC-QLQ-C30). It includes 17 items resulting in a symptom subscale and an impact subscale.

- Change from Baseline in Symptoms, Functioning, and Health-related Quality of Life (HRQoL) as Assessed by EORTC-QLQ-C30 [Time Frame: Up to 7 years 2 months]

Change from baseline in symptoms, functioning, and HRQoL as assessed by EORTC-QLQ-C30 will be reported. The EORTC-QLQ-C30 Version 3 includes 30 items that make up 5 functional scales (physical, role, emotional, cognitive, and social), 1 global health status scale, 3 symptom scales (pain, fatigue, and nausea or vomiting), and 5 single symptom items (dyspnea, insomnia, appetite loss, constipation, and diarrhea) and a single impact item (financial difficulties). The recall period is 7 days ("past week"), and responses are reported using a verbal and numeric rating scales. The item and scale scores are transformed to a 0 to 100 scale. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high or healthy level of functioning and a high score for the global health status represents high HRQoL, but a high score for a symptom scale or item represents a high level of symptomatology or problems.

- Change from Baseline in Symptoms, Functioning, and Health-related Quality of Life (HRQoL) as Assessed by EQ-5D-5L [Time Frame: Up to 7 years 2 months]

Change from baseline in symptoms, functioning, and HRQoL as assessed by EQ-5D-5L will be reported. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain or discomfort, and anxiety or depression plus a visual analog scale rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

- Change from Baseline in Symptoms, Functioning, and Health-related Quality of Life (HRQoL) as Assessed by PGI-S [Time Frame: Up to 7 years 2 months]

Change from baseline in symptoms, functioning, and HRQoL as assessed by PGI-S will be reported. The PGI-S will be used as an anchor, external criterion, to determine meaningful change in scores for the MySIm-Q and EORTC-QLQ-C30 in this population. The response options are presented as a 5-point verbal rating scale from “none” to “very severe."

- Change from Baseline in Symptoms, Functioning, and Health-related Quality of Life (HRQoL) as Assessed by Epstein Taste Survey [Time Frame: Up to 7 years 2 months]

Change from baseline in symptoms, functioning, and HRQoL as assessed by epstein taste survey will be reported. The epstein taste survey consists of 17 items from the full 71 item PRO instrument, specific to taste changes. developed for use in patients with head and neck cancer as a composite of the Vanderbilt Head and Neck Symptom Survey.

- Percentage of Participants With Meaningful Improvement in HRQoL as Assessed by EORTC-QLQ-C30 [Time Frame: Up to 7 years 2 months]

Percentage of participants with meaningful improvement in HRQol as assessed by EORTC-QLQ-C30 will be reported. The EORTC-QLQ-C30 Version 3 includes 30 items that make up 5 functional scales (physical, role, emotional, cognitive, and social), 1 global health status scale, 3 symptom scales (pain, fatigue, and nausea or vomiting), and 5 single symptom items (dyspnea, insomnia, appetite loss, constipation, and diarrhea) and a single impact item (financial difficulties). The recall period is 7 days ("past week"), and responses are reported using a verbal and numeric rating scales. The item and scale scores are transformed to a 0 to 100 scale. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high or healthy level of functioning and a high score for the global health status represents high HRQoL, but a high score for a symptom scale or item represents a high level of symptomatology or problems.

Arms	**Assigned Interventions**
Experimental: Arm A: Talquetamab + Pomalidomide (Tal-P) Participants will receive talquetamab as subcutaneous (SC) injections; pomalidomide will be self-administered as a single dose orally; dexamethasone may be given orally or	Drug: Talquetamab Talquetamab will be administered as a SC injection. Other Name: JNJ-64407564 Other Name: Talvey Drug: Pomalidomide

intravenously as a pretreatment medication and study drug.	Pomalidomide will be administered orally. Other Name: Pomalyst Other Name: Imnovid Drug: Dexamethasone Dexamethasone will be administered either orally or intravenously.
Experimental: Arm B: Talquetamab + Teclistamab (Tal-Tec) Participants will receive teclistamab in combination with talquetamab both as SC injection; dexamethasone may be given orally or intravenously as a pretreatment medication and study drug.	Drug: Talquetamab Talquetamab will be administered as a SC injection. Other Name: JNJ-64407564 Other Name: Talvey Drug: Teclistamab Teclistamab will be administered as a SC injection. Other Name: JNJ-64007957 Other Name: Tecvayli Drug: Dexamethasone Dexamethasone will be administered either orally or intravenously.
Active Comparator: Arm C: Elotuzumab+ Pomalidomide+Dexamethasone (EPd) or Pomalidomide+Bortezomib+Dexamethasone (PVd) Participants will either receive elotuzumab intravenous (IV) injection in combination with pomalidomide and dexamethasone orally; or pomalidamide orally in combination with bortezomib SC injection and dexamethasone orally as per investigator	Drug: Pomalidomide Pomalidomide will be administered orally. Other Name: Pomalyst Other Name: Imnovid Drug: Elotuzumab Elotuzumab will be administered intravenously. Other Name: Empliciti Drug: Dexamethasone Dexamethasone will be administered either orally or intravenously.

choice. Dexamethasone will be administered as a pretreatment medication.	Drug: Bortezomib Bortezomib will be administered as a SC injection. Other Name: Velcade

[0282] Inclusion Criteria:

[0283] - Documented multiple myeloma as defined by the criteria below: (a) multiple myeloma diagnosis according to the international myeloma working group (IMWG) diagnostic criteria (b) measurable disease at screening as assessed by central laboratory, defined by any of the following: (i) serum M-protein level greater than or equal to (>=) 0.5 gram per deciliter (g/dL); or (ii) urine M-protein level >= 200 milligram (mg) per 24 hours; or (iii) light chain multiple myeloma without measurable M-protein in the serum or the urine: serum immunoglobulin (Ig) free light chain (FLC) >= 10 milligrams per deciliter (mg/dL) and abnormal serum Ig kappa lambda FLC ratio

- Relapsed or refractory disease as defined below: a) Relapsed disease is defined as an initial response to prior treatment, followed by confirmed progressive disease (PD) by IMWG criteria greater than (>) 60 days after cessation of treatment. b) Refractory disease is defined as less than (<) 25 percent (%) reduction in M-protein or confirmed PD by IMWG criteria during previous treatment or less than or equal to (<=) 60 days after cessation of treatment

- Documented evidence of PD or failure to achieve a minimal response to the last line of therapy based on investigator's determination of response by IMWG criteria on or after their last regimen

- Have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 at screening and immediately prior to the start of administration of study treatment

-A participant must agree not to be pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 6months after the last dose of study treatment

[0284] Exclusion Criteria:

[0285] - Contraindications or life-threatening allergies, hypersensitivity, or intolerance to any study drug or its excipients

- Stroke, transient ischemic attack, or seizure within 6 months prior to signing informed

consent form (ICF)

- Major surgery or had significant traumatic injury within 2 weeks prior to the start of administration of study treatment, or will not have fully recovered from surgery, or has major surgery planned during the time the participant is expected to be treated in the study or within 2 weeks after administration of the last dose of study treatment
- A maximum cumulative dose of corticosteroids of >=140 mg of prednisone or equivalent within 14-day period before the first dose of study drug
- Known active central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of multiple myeloma. If either is suspected, negative whole brain magnetic resonance imaging (MRI) and lumbar cytology are required

Example 3: A Phase 3 Randomized Study Comparing Talquetamab SC in Combination With Daratumumab SC and Pomalidomide (Tal-DP) or Talquetamab SC in Combination With Daratumumab SC (Tal-D) Versus Daratumumab SC, Pomalidomide and Dexamethasone (DPd), in Participants With Relapsed or Refractory Multiple Myeloma who Have Received at Least 1 Prior Line of Therapy (MonumenTAL-3; NCT05455320)

[0286] Objectives

[0287] The primary objective of this study is to compare the efficacy of talquetamab SC in combination with daratumumab SC and pomalidomide (Tal-DP; Arm A) and talquetamab SC in combination with daratumumab SC (Tal-D; Arm C) with that of daratumumab SC in combination with pomalidomide and dexamethasone (DPd; Arm B) as assessed by PFS, respectively.

[0288] This is a multicenter, randomized, open-label, Phase 3 study to determine whether Tal-DP (Arm A) and Tal-D (Arm C) have better efficacy than DPd (Arm B), respectively, in participants with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy including a PI and lenalidomide. The study will be conducted in 3 phases for each participant: Screening (28 days), Treatment (until confirmed progressive disease, death, intolerable toxicity, withdrawal of consent, or end of the study, whichever occurs first), and Posttreatment Follow-up (until death, withdrawal of consent, loss to followup, or end of the study, whichever occurs first). In addition to the primary endpoint (PFS) and key secondary endpoints (overall response, CR or better, MRD-negative CR and OS), data will be collected to evaluate VGPR or better; PFS2; safety profile (ie, incidence and severity of AEs); PK and

immunogenicity for talquetamab SC and daratumumab SC; PROs; MRU; and other exploratory endpoints. An Independent Data Monitoring Committee will be commissioned for this study to review data from the interim analyses and cumulative safety data. Approximately 810 participants will be randomized in a 1:1:1 ratio to Tal-DP (Arm A), DPd (Arm B) and Tal-D (Arm C).

[0289] Description of Study Treatment & Efficacy Evaluations

[0290] Efficacy assessments will occur per IMWG criteria (2016) as defined in the protocol using data from serum, urine, bone marrow, and imaging (if applicable). Responses or progression will be evaluated by investigators, use of a validated algorithm, and by an IRC.

[0291] Study treatment will be administered in 28-day cycles for all treatment arms, as follows.

[0292] Arm A: Tal-DP (28-day cycle)

[0293] Talquetamab subcutaneous (SC) Step-up Dose 1: 10 µg/kg; Step-up Dose 2: 60 µg/kg; Step-up Dose 3: 400 µg/kg; treatment dose 800 µg/kg:

- Cycle 1: Step-up Dose 1: Day 2; Step-up Dose 2: Day 4 (+2 days); Step-up Dose 3: Day 8 (+2 days); treatment dose: Day 15 (+2 days)
    - Note: Step-up Dose 2 and Step-up Dose 3 may be administered on Day 3 and Day 7, respectively with Sponsor Approval
- Cycles 2-4: treatment dose on Days 1 and 15
- Cycles 5-6: Days 1 and 15 or if confirmed VGPR or better, may change to Q4W dosing (Day 1 only)
- From Cycle 7: Q4W dosing (Day 1 only) for participants with response of confirmed PR or better. All other participants continue Q2W dosing (Days 1 and 15) until response of confirmed PR or better is achieved.

[0294] Daratumumab SC 1800 mg:

- Cycles 1-2: Days 1, 8, 15 and 22
- Cycles 3-6: Days 1 and 15
- Subsequent cycles: Day 1

[0295] Pomalidomide (oral) 2 mg:

- Cycle 2 and subsequent cycles: Days 1-21

[0296] Arm B: DPd (28-day cycle)

[0297] Daratumumab SC 1800 mg:

- Cycles 1-2: Days 1, 8, 15 and 22
- Cycles 3-6: Days 1 and 15
- Subsequent cycles: Day 1

[0298] Pomalidomide (oral) 4 mg:

- All cycles: Days 1-21

[0299] Dexamethasone (oral/IV) 40 mg weekly (<75 years of age) or 20 mg weekly (<75 years of age with BMI <18.5 or ≥75 years of age)

- All cycles: Days 1, 8, 15, 22

[0300] Arm C: Tal-D (28-day cycle)

[0301] Talquetamab subcutaneous (SC) Step-up Dose 1: 10 µg/kg; Step-up Dose 2: 60 µg/kg; Step-up Dose 3: 400 µg/kg; treatment dose 800 µg/kg:

- Cycle 1: Step-up Dose 1: Day 2; Step-up Dose 2: Day 4 (+2 days); Step-up Dose 3: Day 8 (+2 days); treatment dose: Day 15 (+2 days)
    - Note: Step-up Dose 2 and Step-up Dose 3 may be administered on Day 3 and Day 7, respectively with Sponsor Approval
- Cycles 2-4: treatment dose on Days 1 and 15
- Cycles 5-6: Days 1 and 15 or if confirmed VGPR or better, may change to Q4W dosing (Day 1 only)
- From Cycle 7: Q4W dosing (Day 1 only) for participants with response of confirmed PR or better. All other participants continue Q2W dosing (Days 1 and 15) until response of confirmed PR or better is achieved.

[0302] Daratumumab SC 1800 mg:

- Cycles 1-2: Days 1, 8, 15 and 22
- Cycles 3-6: Days 1 and 15
- Subsequent cycles: Day 1

[0303] Justification for Dose

[0304] The proposed dose for talquetamab SC (10, 60 and 400 µg/kg step-up doses followed by 800 µg/kg SC biweekly treatment dose) was selected based on the PK, PD, safety, and efficacy findings from the Phase 1 (Part 1 and 2) portion of the MonumenTAL-1 trial (talquetamab monotherapy) and the Phase 1b TriMM-2 clinical trial (talquetamab combination therapy). TEAEs were tolerable and manageable. CRS was generally low grade **and neurotoxicity events were rare. Talquetamab monotherapy at 800 µg/kg SC biweekly** dosing is effective in terms of overall response, and time to first response.

[0305] Preliminary pharmacokinetic (PK) results showed that talquetamab trough levels following the first 800 µg/kg SC administration were comparable to or higher than the maximum EC90 values identified in an ex vivo cytotoxicity assay. This assay assessed the ability of talquetamab to induce killing using mononuclear cells from the bone marrow samples of multiple myeloma patients in co-culture with T cells from healthy donors. The trough concentrations at steady state were also comparable to or higher than the maximum EC90. Overall, the talquetamab SC dose schedule of 800 µg/kg biweekly is estimated to provide comparable exposure and hence comparable safety with the 400 µg/kg talquetamab weekly dose schedule. Response data in this study are preliminary but suggest a promising effect of talquetamab in combination with daratumumab SC.

[0306] In the current study, the frequency of dosing may be decreased at the investigator's discretion to Q4W for talquetamab starting at C5D1 for participants with response of confirmed VGPR or better. For participants with response of confirmed PR or better, talquetamab dosing must be switched to Q4W starting at C7D1.

[0307] The median concentration-time profile following Q4W dosing at C5D1 or C7D1 is estimated to be above the maximum concentration associated with the EC90 value identified in an ex vivo cytotoxicity assay and is expected to be sufficient to maintain efficacy in a low tumor burden setting. Additionally, a dose-response relationship was observed for talquetamab-specific AEs (skin, oral, and nail toxicity) based on a preliminary safety exposure-response analysis. Therefore, participants who switch to a lower dose after becoming responders for a certain period may benefit from a lower (or non-worsening) incidence of AEs.

[0308] Data from Study 64407564MMY1001 (MonumenTAL-1) has shown a median time to first response of 1.2 months and a median time to best response of 2.2 months for participants treated with talquetamab 800 µg/kg SC Q2W. In Phase 1 of MonumenTAL-1, participants enrolled in Cohort 33 received treatment with talquetamab 800 µg/kg SC Q2W until response of confirmed PR or better and then decreased the frequency of talquetamab dosing to Q4W. Of the 12 participants enrolled into this cohort, 10 achieved a response of PR or better and had a subsequent change in dosing frequency to 800 µg/kg SC Q4W, and 2 participants had best response of PD. Dose frequency changes for the 10 participants with response of PR or better occurred on Day1 of Cycles 3 through 5. Eight of the 10 participants maintained or deepened their response after the change to Q4W.

[0309] The proposed Q4W dosing schedule of talquetamab would maintain efficacy by balancing maximal reduction of disease burden with biweekly dosing in the initial 6 cycles of treatment with participant convenience and reduced exposure with Q4W dosing from Cycle 7 onward for participants with response of confirmed PR or better (or as early as Cycle 5 for participants who have achieved a confirmed response of VGPR or better).

[0310] **Outcome Measures**

[0311] The primary outcome measure is progression-free survival (PFS). PFS is defined as time from the date of randomization to the first documentation of disease progression, or death due to any cause, whichever is reported first.

[0312] Secondary outcome measures include the following:

Overall Response (Partial Response [PR] or Better)	Overall response (PR or better) is defined as percentage of participants who have a PR or better per International Myeloma Working Group (IMWG) criteria.
Very Good Partial Response (VGPR) or Better Rate	VGPR or better rate is defined as the percentage of participants who achieve a VGPR or better according to IMWG response criteria.
Complete Response (CR) or Better Rate	CR or better rate is defined as the percentage of participants who achieve CR or better according to IMWG response criteria.
Overall Minimal Residual Disease (MRD) Negative CR	MRD-negative CR is defined as proportion of participants with CR or stringent CR who achieve MRD negativity at a threshold of 10^-5 at any timepoint after the first dose of study drug and before disease progression or start of subsequent antimyeloma therapy.

Overall Survival (OS)	OS is defined as the time from the date of randomization to the date of the participant's death.
Progression-free Survival on Next-line Therapy (PFS2)	PFS2 is defined as the time interval between the date of randomization and date of event, which is defined as progressive disease as assessed by investigator on the first subsequent line of antimyeloma therapy, or death from any cause, whichever occurs first.
Time to Next Therapy (TTNT)	TTNT is defined as the time from randomization to the start of subsequent antimyeloma treatment.

[0313] Participation Criteria

[0314] Inclusion criteria include the following:

- Documented multiple myeloma as defined: a) Multiple myeloma diagnosis according to the International Myeloma Working Group (IMWG) diagnostic criteria and b) Measurable disease at screening as defined by any of the following: i) Serum M-protein level greater than or equal to (>=) 0.5 grams per deciliter (g/dL) (central laboratory); ii) Urine M-protein level >= 200 milligram (mg) per 24 hours (central laboratory); iii) Light chain multiple myeloma without measurable M-protein in the serum or the urine: serum immunoglobulin free light chain >= 10 milligram per deciliter (mg/dL) (central laboratory), and abnormal serum immunoglobulin kappa lambda free light chain ratio
- Relapsed or refractory disease as defined by: i) Relapsed disease is defined as an initial response to prior treatment, followed by confirmed progressive disease by IMWG criteria greater than (>) 60 days after cessation of treatment; ii) Refractory disease is defined as less than (<) 25 percent (%) reduction in monoclonal paraprotein (M-protein) or confirmed progressive disease by IMWG criteria during previous treatment or less than or equal to (<=) 60 days after cessation of treatment
- Received at least 1 prior line of antimyeloma therapy including a proteasome inhibitor (PI) and lenalidomide. Participants who have received only 1 prior line of antimyeloma therapy must be considered lenalidomide-refractory (that is, have

demonstrated progressive disease by IMWG criteria on or within 60 days of completion of lenalidomide-containing regimen). Participants who have received >=2 prior lines of antimyeloma therapy must be considered lenalidomide exposed

- Documented evidence of progressive disease based on investigator's determination of response by the IMWG criteria on or after their last regimen
- Have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 at screening and immediately prior to the start of administration of study treatment

[0315] Exclusion criteria include the following:

- Contraindications or life-threatening allergies, hypersensitivity, or intolerance to study drug excipients
- Disease is considered refractory to an anti-cluster of differentiation 38 (CD38) monoclonal antibody as defined per IMWG consensus guidelines (progression during treatment or within 60 days of completing therapy with an anti-CD38 monoclonal antibody)
- Received prior pomalidomide therapy
- A maximum cumulative dose of corticosteroids to >=140 milligrams (mg) of prednisone or equivalent within 14-day period before the first dose of study drug
- Known active central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of multiple myeloma. If either is suspected, negative whole brain magnetic resonance imaging (MRI) and lumbar cytology are required
- Plasma cell leukemia (per IMWG criteria) at the time of screening, Waldenström's macroglobulinemia, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS syndrome), or primary amyloid light chain amyloidosis

Example 4: A Phase 3 Randomized Study Comparing Teclistamab in Combination with Daratumumab SC and Lenalidomide (Tec-DR) versus Daratumumab SC, Lenalidomide, and Dexamethasone (DRd), and Talquetamab in Combination with Daratumumab SC and Lenalidomide (Tal-DR) versus DRd, in Patients with Newly Diagnosed Multiple Myeloma Who are Either Ineligible or not Intended for Autologous Stem Cell Transplant as Initial Therapy (MajesTEC-7)

[0316] This is a randomized, 3-arm, open-label, multicenter, Phase 3 study in adult participants with newly diagnosed multiple myeloma according to the IMWG diagnostic

criteria who are ineligible or not intended for ASCT as initial therapy (preceded by a Safety Run-in part). The study will be conducted in 3 phases: Screening (up to 28 days), Treatment (until confirmed progressive disease, death, intolerable toxicity, loss to follow-up, withdrawal of consent, or end of the study, whichever occurs first), and Follow-up (until withdrawal of consent, loss to follow-up, death, or end of study, whichever occurs first). The primary objective is to compare the efficacy of Tec-DR versus DRd and Tal-DR versus DRd in terms of PFS and 12-month MRD-negative CR.

[0317] Description of Study Treatment & Efficacy Evaluations

[0318] Efficacy assessments will occur per IMWG criteria (2016) as defined in the protocol, using data from serum, urine, bone marrow, and imaging. Responses or progression will be evaluated by the investigator and through use of a validated computerized algorithm.

Tec-DR (Randomized Part)

Study Treatment	Dose Schedule (each cycle = 28 days)
Teclistamab SC	C1: 2 step-up doses (0.06 and 0.3 mg/kg) on Days 2 and 4 followed by treatment doses (1.5 mg/kg) on Days 8 and 15 C2+: Q4W treatment doses (3 mg/kg) on Day 1
Daratumumab SC 1800 mg	C1-2: weekly on Days 1, 8, 15, and 22 C3-6: Q2W on Days 1 and 15 C7+: Q4W on Day 1
Lenalidomide oral 25 mg*	C2+: D1-21
Dexamethasone oral/IV 20 mg**	C2-3: weekly on Days 1, 8, 15, and 22

* Lenalidomide dose may need to be adjusted for participants with reduced CrCl.

** Dexamethasone (16 mg) will be administered as pretreatment medication on Days 1, 2, 4, and 8 of Cycle 1.

Tal-DR (Randomized Part)

Study Treatment	Dose Schedule (each cycle = 28 days)
Talquetamab SC	C1: 3 step-up doses (0.01, 0.06, and 0.4 mg/kg) on Days 2, 4, and 8 followed by treatment dose (0.8 mg/kg) on Day 15 C2+: Q4W treatment doses (0.8 mg/kg) on Day 1
Daratumumab SC 1800 mg	C1-2: weekly on Days 1, 8, 15, and 22 C3-6: Q2W on Days 1 and 15 C7+: Q4W on Day 1
Lenalidomide oral 25 mg*	C2+: D1-21
Dexamethasone oral/IV 20 mg**	C2-3: weekly on Days 1, 8, 15, and 22

* Lenalidomide dose may need to be adjusted for participants with reduced CrCl.

** Dexamethasone (16 mg) will be administered as pretreatment medication on Days 1, 2, 4, and 8 of Cycle 1.

DRd – Randomized Part

Study Treatment	Cycle (each cycle=28 days)	Dose Schedule
Daratumumab SC (1800 mg)	Cycles 1 and 2	Weekly dose on Days 1, 8, 15, 22
	Cycles 3 to 6	Q2W dose on Days 1 and 15
	Cycles 7+	Q4W dosing on Day 1
Lenalidomide PO (25 mg)*	Cycles 1+	Days 1-21
Dexamethasone PO/IV (40 mg)**	Cycles 1+	Weekly dose on Days 1, 8, 15, and 22

IV=intravenous; PO=per os (oral); Q2W=every other week; SC=subcutaneous
* Lenalidomide dose may need to be adjusted for participants with reduced CrCl
** For participants >75 years of age or with BMI <18.5 kg/m2, dexamethasone may be administered at a dose of 20 mg.

[0319] Justification for Talquetamab Dose

[0320] Talquetamab and daratumumab will be initiated in Cycle 1 and lenalidomide only added in Cycle 2 after the step-up phase. The talquetamab dose schedule for the Randomized Part of the study will consist of 3 step-up doses (0.01, 0.06, and 0.4 mg/kg) on Cycle 1 Days 2, 4, and 8 followed by the treatment dose of 0.8 mg/kg dose at Cycle 1 Day 15. Starting from Cycle 2, dosing will be 0.8 mg/kg on Day 1 of each cycle.

[0321] The proposed dose for talquetamab SC was selected based on the PK, pharmacodynamic, safety,and efficacy findings from the a subset of the pivotal RP2D population in MonumtanTAL-1 who switched to less frequent dosing and the Phase 1 portion of the study (monotherapy), the Phase 1b TriMM-2 clinical study (combination therapy in the relapsed/refractory population), and early data from MonumenTAL-2 (combination therapy in the relapsed/refractory and newly diagnosed populations). TEAEs were tolerable and manageable. CRS was generally low grade and neurotoxicity events were rare.

[0322] Additionally, data from MonumenTAL-1 demonstrates that participants who switched to less frequent dosing after achieving response with talquetamab monotherapy have improved PFS compared with the overall pivotal population and experienced fewer study drug-related TEAEs and Grade 3 or 4 TEAEs after switching and experienced improve resolution of on-target-related toxicity (eg, oral, skin, and rash AEs).

[0323] Similarly, data for the combination of Tal-DR in newly diagnosed multiple myeloma participants from MonumenTAL-2 demonstrate that this regimen is well tolerated with low rates of discontinuations and emerging data from MonumenTAL-2 show high response rates with DR in combination with 0.8 mg/kg Q4W talquetamab in participants with

newly diagnosed multiple myeloma. Of note, preliminary efficacy data suggest that the 0.8 mg/kg Q4W dosing schedule has similar overall response rate and rate of VGPR as the more intense schedule of 0.6 mg/kg Q2W.

[0324] Overall, the above data indicate that reducing dosing after response had no adverse impact on efficacy with a potential reduction in toxicity. Since the experimental regimen in MajesTEC-7 includes robust background therapy (DRd), and in light of a potential improvement of tolerability and reduction of talquetamab-associated toxicities, the lower dose of 0.8 mg/kg monthly has been elected for the Randomized Part of MajesTEC-7.

[0325] PK simulations showed that talquetamab trough levels following the first 0.8 mg/kg SC administration were comparable or higher than the maximum EC90 values identified in an ex vivo cytotoxicity assay. This assay assessed the ability of talquetamab to induce killing using mononuclear cells from the bone marrow samples of multiple myeloma patients in co-culture with T cells from healthy donors. The trough concentrations at steady state were also comparable to or higher than the maximum EC_{90}.

[0326] Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of Tec-DR versus DRd and Tal-DR versus DRd	Dual Primary Endpoints: • PFS • Sustained MRD-negative CR **(duration ≥ 12 months)**
Secondary	
• To further compare the efficacy of Tec-DR versus DRd	• VGPR or better • CR or better • MRD-negative CR • PFS2 • OS
• To assess the safety and tolerability of teclistamab when administered in combination with DR	• Incidence and severity of AEs, laboratory results, and other safety parameters
• To characterize PK of teclistamab	• PK parameters using population PK approach

Objectives	Endpoints
• To assess the immunogenicity of teclistamab	• Presence of ADAs to teclistamab
• To assess participant's symptoms, functioning, and HRQoL with Tec-DR versus DRd	• Change from baseline in symptoms, functioning, and HRQoL • Time to sustained worsening in symptoms, functioning, and overall HRQoL
Exploratory	
• To evaluate and explore pharmacodynamics biomarkers of antimyeloma and immune activity in participants treated with Tec-DR and DRd • To explore the relationship between PK, pharmacodynamics activity, AEs, and clinical response in participants treated with Tec-DR and DRd. • To explore the relationship between MRD negativity with duration and depth of clinical response in participants treated with Tec-DR and DRd. • To explore predictive biomarkers of response and resistance, including prognostic and disease markers at baseline, during treatment, and in relation to efficacy parameters • To identify patient subgroups that could respond differently to Tec-DR and DRd. • To evaluate MRU • To explore time to symptomatic progression in both treatment arms • To explore time to next treatment	

Abbreviations: AE=adverse event; CR=complete response; IMWG=International Myeloma Working Group; mBCAM=membrane BCMA; MRD=minimal residual disease; rHuPH20=recombinant human hyaluronidase PH20 enzyme; PR=partial response; sBCMA=soluble BCMA; sCR=stringent complete response; VGPR=very good partial response

[0327] Participation Criteria

[0328] Inclusion Criteria include the following:

- Have a diagnosis of multiple myeloma according to the International Myeloma Working Group (IMWG) diagnostic criteria;

- Be newly diagnosed and not considered a candidate for high-dose chemotherapy with autologous stem cell transplant (ASCT) due to: ineligible due to advanced age OR; ineligible due to the presence of comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with ASCT OR; deferral of high-dose chemotherapy with ASCT as initial treatment;
- Have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2;
- A participant must agree not to be pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study treatment;
- A participant must agree not to plan to father a child while enrolled in this study or within 100 days after the last dose of study treatment.

[0329] Exclusion Criteria include the following:

- Received any prior therapy for multiple myeloma or smoldering myeloma other than a short course of corticosteroids (not to exceed 40 milligrams [mg] of dexamethasone, or equivalent per day for a maximum of 4 days, total of 160 mg dexamethasone or equivalent). In addition, received a cumulative dose of systemic corticosteroids equivalent to greater than or equals to (>=)20 mg of dexamethasone during the Screening Phase
- Had plasmapheresis within 28 days of randomization
- Had a stroke, transient ischemic attack, or seizure within 6 months prior to randomization
- Known allergies, hypersensitivity, or intolerance to teclistamab or talquetamab excipients
- Known contraindications to the use of daratumumab or lenalidomide per local prescribing information
- Myeloma Frailty Index of >=2 with the exception of participants who have a score of 2 based on age alone

Example 5: Talquetamab (tal) + daratumumab (dara) + pomalidomide (pom) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Results from the phase 1b TRIMM-2 study

[0330] **Introduction:** Tal is the first approved GPRC5D X CD3 bispecific antibody (BsAb) for triple-class exposed RRMM. The immunomodulatory effects of dara + pom may potentiate the efficacy of tal. Initial TRIMM-2 results showed that subcutaneous (SC) dara + SC tal 0.4 mg/kg weekly (QW) or 0.8 mg/kg every other week (Q2W) had promising efficacy, with a safety profile consistent with the respective monotherapies. Provided below are results from pts who received tal + dara + pom in TRIMM-2.

[0331] **Methods:** Pts had MM, ≥3 prior lines of therapy (LOT; including a proteasome inhibitor [PI] and immunomodulatory drug [IMiD]) or were double refractory to a PI and IMiD and had not received anti-CD38 therapy in ≤90 days. Pts received tal 0.4 mg/kg QW or 0.8 mg/kg Q2W + dara 1800 mg + pom 2 mg (starting cycle 2). AEs were graded per CTCAE v5.0; cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) were graded per ASTCT guidelines. Responses were assessed per IMWG criteria.

[0332] **Results:** As of April 10, 2024, 77 pts received tal + dara + pom (median follow-up: 17.5 months [mo]). Median prior LOT was 6 over a median of 6.8 years since diagnosis. At baseline, 26.2% had high-risk cytogenetics and 23.4% had extramedullary disease. Most pts were penta-drug exposed (68.8%) and triple-class refractory (77.9%). Prior treatments included anti-CD38 (93.5% [83.1% refractory]; dara (90.9% [80.5%]), IMiD (100% [97.4%]; pom, 83.1% [75.3%]), chimeric antigen receptor-T cell (31.2%), and BsAb (39.0% [37.7%]) therapies. Median time since last dara exposure was 474 days and 385 days for pom. There were no dose-limiting toxicities. All pts had ≥1 AE (gr 3/4 94.8%), most commonly dysgeusia (79.2%; gr 3/4: NA), neutropenia (77.9%; gr 3/4: 68.8%), CRS (74.0%; all gr 1/2), dry mouth (64.9%; gr 3/4: 2.6%), and fatigue (57.1%; gr 3/4: 5.2%). Median onset of CRS was 1 day after tal; median duration was 2 days. ICANS occurred in 3.9% (gr 3/4: 1.3%). Infections occurred in 74.0% (gr 3/4: 29.9%); onset of most gr ≥3 infections occurred within the first 6 months (18/23 events). Overall, 5.8% of pts discontinued tal due to AEs. Two pts died due to AEs, including 1 gr 5 sepsis. ORR was 81.8%; 53.2% had a complete response or better. Responses were deep and durable in anti-CD38 refractory and prior T-cell redirection exposed pts. Median DOR was 22.1 mo (95% CI, 13.6–27.0). Median time to first response was 1.0 mo (range, 0.9–6.7). Median PFS was 15.5 mo (95% CI, 11.7–24.4). Preliminary

data showed that tal serum concentrations were generally within the same range as with tal monotherapy.

[0333] **Conclusion:** In heavily pretreated pts with RRMM who were mostly dara and pom refractory, tal + dara + pom showed promising depth and durability of response. The safety profile was consistent with the known safety profiles of each respective agent. These results support the versatility of tal as a combination partner and warrant further investigation of tal in combination with dara or pom

Example 6: Cytokine Release Syndrome in Patients Receiving Alternative Step-Up Doses of Talquetamab for Relapsed/Refractory Multiple Myeloma: Results from the Phase 1/2 MonumenTAL-1 Study

[0334] **Introduction:** Talquetamab (tal) is the first GPRC5D×CD3 bispecific antibody approved for the treatment of patients (pts) with relapsed/refractory multiple myeloma (RRMM). Cytokine release syndrome (CRS) is a common adverse event reported with T-cell redirecting bispecific antibodies. To mitigate the risk of CRS, pts receive step-up doses (SUDs). In MonumenTAL-1, for the tal 0.4 mg/kg weekly (QW) and 0.8 mg/kg every other week (Q2W) approved doses, pts received 2 (0.01 and 0.06 mg/kg) or 3 (0.01, 0.06, and 0.4 mg/kg) SUDs, respectively. With 3 SUDs in the tal 0.8 mg/kg Q2W cohort, CRS occurred in 74.5% of pts; most CRS events occurred during SUDs and cycle 1. Patients were monitored for 48 hours after each SUD and first full treatment dose. This analysis evaluated the impact of alternative, fewer SUDs in the talquetamab Q2W schedule on key parameters of CRS.

[0335] **Methods:** Pts from phase 1 of MonumenTAL-1 (NCT03399799) receiving the 0.8 mg/kg Q2W approved dose were included in the analysis; patients could switch to 0.8 mg/kg monthly at confirmed partial response (PR) or better. Pts received one of two alternative SUD schedules: 0.03 mg/kg followed by 0.2 mg/kg (cohort 34; n=6) and 0.06 mg/kg followed by 0.4 mg/kg (cohort 35; n=12). Timing of administration was 24-72 hours between SUDs and first treatment dose, with monitoring 48 hours post-first treatment dose. CRS was graded by ASTCT criteria; all other adverse events were graded by CTCAE criteria (v4.03).

[0336] **Results:** Across cohorts 34 and 35, a total of 18 patients were included in the analysis, with a median follow-up (range) of 6.7 months (2.2–9.9). Most patients had high-risk cytogenetics (n=10/18), were triple-class refractory (n=11/18), and were refractory to their last line of therapy (n=11/18); extramedullary plasmacytomas were present in 3/18 patients.

[0337] CRS occurred in all (n=6/6) patients in cohort 34 and in 91.7% (n=11/12) of patients in cohort. Although rates of grade 1 and 3 events were consistent between the alternative SUD cohorts and the global Q2W cohort (median follow-up [range]: 23.4 months [0.2–37.4]), rates of grade 2 events were higher with the alternative SUD schedules. Multiple CRS events occurred in 16.7% (n=1/6) and 25.0% (n=3/12) of patients in cohorts 34 and 35, respectively, and in 33.1% (n=51/154) of patients in the global Q2W cohort. CRS events predominantly occurred during SUDs across all cohorts, as shown in the following table:

	SUDs			**C1D1**
Global Q2W cohort approved SUDs, mg/kg	**0.01**	**0.06**	**0.4**	**0.8**
CRS, n (%)	41/154 (26.6)	63/154 (40.9)	56/154 (36.4)	22/154 (14.3)
Cohort 34 SUDs, mg/kg	**NA**	**0.03**	**0.2**	**0.8**
CRS, n (%)	NA	4/6 (66.7)	3/6 (50.0)	0
Cohort 35 SUDs, mg/kg	**NA**	**0.06**	**0.4**	**0.8**
CRS, n (%)	NA	9/12 (75.0)	5/12 (41.7)	1/12 (8.3)

[0338] Most CRS events occurred during the first SUD for the alternative SUD cohorts (66.7% and 75.0%) vs during the second SUD for the global Q2W cohort (40.9%). In the global Q2W cohort, more CRS events occurred during cycle 1 (n=29) and after cycle 2 (n=5) vs the alternative SUD cohorts (both n=1). Median time to CRS onset and median duration of CRS were the same across alternative SUD and global cohorts (2 days each measure). Across alternative SUD cohorts and the global Q2W cohort, respectively, 77.8% and 37.0% of patients received tocilizumab treatment for CRS. No patients who received tocilizumab had a subsequent grade 2 event. No patients discontinued talquetamab due to CRS in the alternative SUD cohorts compared with 1 patient in the global Q2W cohort.

[0339] No patients in cohort 34 experienced neurotoxicity. One (8.3%) patient in cohort 35 experienced grade 1 neurotoxicity during the first SUD and concurrently with CRS; this event resolved and did not lead to discontinuation of talquetamab. There were no discontinuations of talquetamab or deaths due to treatment-emergent adverse events in the alternative SUD cohorts.

[0340] As of July 31, 2024, overall response rate (ORR) was 83.3% in each of the alternative SUD cohorts. ORR appeared higher than in the global Q2W cohort with the caveat of small patient numbers in the alternative SUD cohorts. Time to first response

(range) was 1.2 months (1.1–2.1) in cohort 34 and 1.2 months (0.3–4.2) in cohort 35. Time to best response (range) was 2.1 months (1.1–4.7) in cohort 34 and 2.7 months (1.1–5.5) in cohort 35.

[0341] Preliminary analysis showed that starting from C1D1, talquetamab serum exposure was comparable between the alternative SUD cohorts and global Q2W cohort. In cohorts 34 and 35, respectively, the median number of treatment cycles (range) received was 10.0 (4–11) and 5.0 (2–10).

[0342] **Conclusions:** These results showed that the use of fewer SUDs to reach the talquetamab Q2W dose was associated with a higher incidence of grade 2 CRS, suggesting that the approved schedule with 3 SUDs may be more clinically manageable until additional prophylactic measures are investigated. With alternative, fewer SUDs, the proportion of patients with grade 2 CRS was increased in both alternative SUD cohorts compared with the global Q2W cohort. Outside of the CRS profile, no other early safety signals or impact on pharmacokinetics were observed with the alternative SUD schedules. Studies are evaluating use of prophylactic tocilizumab to continue to explore approaches to optimize the SUD schedule to allow safe but efficient use of talquetamab.

Example 7: Prophylactic Tocilizumab ("Toci") to Mitigate Cytokine Release Syndrome in Patients Receiving Talquetamab for Relapsed/Refractory Multiple Myeloma: Results From the Phase 1/2 MonumenTAL-1 Study

[0343] **Introduction:** In the MonumenTAL-1 study, at 25.6–34.6 months median follow-up across cohorts, cytokine release syndrome (CRS) occurred in 73.1–79.0% of patients, among whom, 35.0–47.4% were treated with tocilizumab (toci; ± other interventions). Data suggest that prophylactic toci before BsAb treatment may reduce the incidence and severity of CRS, which may facilitate outpatient administration of step-up doses (SUDs) and improve patient experience. The current analysis evaluated the effects of prophylactic toci on CRS parameters following talquetamab treatment.

[0344] **Methods:** Eligible patients were from phase 2 of MonumenTAL-1 (NCT04634552). Patients had RRMM and received ≥3 prior lines of therapy (LOT; ≥1 proteasome inhibitor [PI], ≥1 immunomodulatory drug [IMiD], and ≥1 anti-CD38 antibody).

[0345] Patients received subcutaneous tal 0.8 mg/kg every other week (Q2W) preceded by step-up (priming) doses of 0.01, 0.06, and 0.3 mg/kg in the prospective exploratory cohort. Toci (8 mg/kg IV dose) was given ~3 hrs before the first tal step-up dose together with

required pretreatments (glucocorticoid, antihistamine, and antipyretic). Dexamethasone (dex; 8 mg PO/IV) was given daily for 2 days after each step-up dose and first full treatment dose. If posttreatment dex was scheduled on a day when premedication with dex was required, only the premedication dose was given.

[0346] CRS and ICANS were graded by American Society for Transplantation and Cellular Therapy criteria; other adverse events (AEs) were graded by Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

[0347] **Results:** Twelve (12) patients were included in the analysis, with median follow-up (range) of 4.4 months (0.3–8.8). Most patients were male (75.0%), and ~42% were Black or African American; patients had a median (range) of 3 (3–10) prior LOT. Two (2) patients (16.7%) received prior B-cell maturation antigen–targeted T-cell redirection therapy (1 chimeric antigen receptor T-cell and 1 BsAb).

[0348] Grade 1 CRS events occurred during SUD through cycle 1 in 2 patients (16.7%); grade 1 CRS events occurred at any time in 3 patients (25.0%). One patient (8.3%) had a recurrent grade 1 CRS event during SUD. Median time to CRS onset was 2.0 days (range, 2–12) and median duration was 2 days (range, 1–6). Late median onset was due to the 1 patient with CRS after cycle 1. All 3 patients received treatment for CRS, including toci (n=2) and paracetamol (n=3).

[0349] Prophylactic toci and post dexamethasone (dex) use appeared to lower CRS incidence and severity across varying levels of disease burden.

[0350] Overall response rate in response-evaluable patients was 70.0% (7/10) in the prophylactic toci cohort, similar to the global 0.8 mg/kg Q2W population (69.5%), although patient numbers are small in the prophylactic toci cohort.

[0351] No increase in rates of neutropenia, infections, or on-target, off-tumor AEs (GPRC5D-related AEs) was observed in the prophylactic toci cohort compared with the MonumenTAL-1 global population. Grade 3/4 neutropenia occurred early in the prophylactic toci cohorts, consistent with early timing in the global cohorts (plateauing around 5–6 months), although numbers are small. Two (16.7%) patients had grade 3/4 infections; both had significant medical history that may have impacted their risk for infection; 1 (8.3%) patient died due to lung infection. One patient (8.3%) with 80% BMPCs developed ICANS (grade 2; concomitant with CRS). One patient (8.3%) discontinued treatment due to AEs (skin desquamation).

[0352] **Conclusions:** Prophylactic toci and increased dex use during SUD appears to be a safe and effective strategy to mitigate the risk of CRS with talquetamab. A single dose of toci before talquetamab and increased dex use post dose reduced the incidence and severity of CRS compared with the overall MonumenTAL-1 population. Similar rates and severity of neutropenia and infections were observed with prophylactic toci use compared with the overall MonumenTAL-1 population. These data support the exploration of outpatient administration of talquetamab SUDs to reduce the burden of hospitalization during initial talquetamab treatment.

CLAIMS

What is claimed is:

1. A method of treating multiple myeloma in a subject in need thereof, comprising administering to the subject a combination therapy comprising a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody and a therapeutically effective amount of pomalidomide.

2. The method of claim 1, wherein the GPRC5DxCD3 bispecific antibody comprises a GPRC5D binding domain comprising the HCDR1 of SEQ ID NO: 4, the HCDR2 of SEQ ID NO: 5, the HCDR3 of SEQ ID NO: 6, the LCDR1 of SEQ ID NO: 7, the LCDR2 of SEQ ID NO: 8 and the LCDR3 of SEQ ID NO: 9, and a CD3 binding domain comprising the HCDR1 of SEQ ID NO: 14, the HCDR2 of SEQ ID NO: 15, the HCDR3 of SEQ ID NO: 16, the LCDR1 of SEQ ID NO: 17, the LCDR2 of SEQ ID NO: 18 and the LCDR3 of SEQ ID NO: 19.

3. The method of claim 1 or 2, wherein the GPRC5DxCD3 bispecific antibody comprises a GPRC5D binding domain comprising a heavy chain variable region (VH) having the amino acid sequence of SEQ ID NO: 10 and a light chain variable region (VL) having the amino acid sequence of SEQ ID NO: 11, and the CD3 binding domain comprises a heavy chain variable region (VH) having the amino acid sequence of SEQ ID NO: 20 and a light chain variable region (VL) having the amino acid sequence of SEQ ID NO: 21.

4. The method of any of claims 1-3, wherein the GPRC5DxCD3 bispecific antibody is an IgG1, an IgG2, an IgG3 or an IgG4 isotype.

5. The method of any of claims 1-4, wherein the GPRC5DxCD3 bispecific antibody is an IgG4 isotype.

6. The method of any of claims 1-5, wherein the GPRC5DxCD3 bispecific antibody comprises one or more substitutions in its Fc region.

7. The method of any of claims 1-6, wherein the GPRC5DxCD3 bispecific antibody is an IgG4 isotype and comprises S228P, F234A and L235A substitutions in its Fc region (according to EU numbering).

8. The method of any of claims 1-7, wherein the GPRC5DxCD3 bispecific antibody is an IgG4 isotype and comprises S228P, F234A, L235A F405L and R409K substitutions in its Fc region (according to EU numbering).

9. The method of any of claims 1-8, wherein the Fc region of the GPRC5D binding arm comprises S228P, F234A and L235A substitutions in its Fc region (according to EU numbering).

10. The method of any of claims 1-9, wherein the Fc region of the CD3 binding arm comprises S228P, F234A, L235A, F405L, and R409K substitutions in its Fc region (according to EU numbering).

11. The method of any of claims 1-10, wherein the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having the amino acid sequence of SEQ ID NO: 23.

12. The method of any of claims 1-10, wherein the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 90% identity to the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having at least 90% identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 90% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 90% identity to the amino acid sequence of SEQ ID NO: 23.

13. The method of any of claims 1-10, wherein the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 95% identity to the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having at least 95% identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 95% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 95% identity to the amino acid sequence of SEQ ID NO: 23.

14. The method of any of claims 1-10, wherein the GPRC5DxCD3 bispecific antibody comprises a first heavy chain (HC1) having at least 98% identity to the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having at least 98% identity to the amino acid sequence of SEQ ID NO: 13, a second heavy chain (HC2) having at least 98% identity to the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having at least 98% identity to the amino acid sequence of SEQ ID NO: 23.

15. The method of any of claims 1-10, wherein the GPRC5DxCD3 bispecific antibody is talquetamab.

16. The method of any of claims 1-15, wherein the subject has relapsed or refractory multiple myeloma myeloma.

17. The method of any of claims 1-16, wherein the subject has received at least two prior lines of therapy.

18. The method of any of claims 1-16, wherein the subject has received at least three prior lines of therapy.

19. The method of any of claims 1-16, wherein the subject has received at least four prior lines of therapy (penta-drug exposed).

20. The method of any of claims 1-16, wherein the subject has received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

21. The method of any of claims 1-16, wherein the subject has received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

22. The method of any of claims 1-21 comprising subcutaneously administering treatment doses of the GPRC5DxCD3 bispecific antibody in an amount of either (i) 0.4 mg/kg weekly (QW), or (ii) 0.8 mg/kg bi-weekly (Q2W).

23. The method of any of claims 1-21 comprising subcutaneously administering treatment doses of the GPRC5DxCD3 bispecific antibody in an amount of 0.4 mg/kg weekly (QW).

24. The method of any of claims 1-21 comprising subcutaneously administering treatment doses of the GPRC5DxCD3 bispecific antibody in an amount of 0.8 mg/kg bi-weekly (Q2W).

25. The method of any of claims 1-24 comprising subcutaneously administering to the subject one or more step-up doses of the GPRC5DxCD3 bispecific antibody prior to administering the first treatment dose of the GPRC5DxCD3 bispecific antibody.

26. The method of any of claims 1-25, comprising subcutaneously administering 2 or 3 step-up doses of the GPRC5DxCD3 bispecific antibody prior to subcutaneously administering the first treatment dose.

27. The method of any of claims 1-26, comprising subcutaneously administering step-up doses of 0.01 mg/kg and 0.06 mg/kg of the GPRC5DxCD3 bispecific antibody prior to subcutaneously administering a treatment dose.

28. The method of any of claims 1-27, comprising subcutaneously administering step-up doses of 0.01 mg/kg, 0.06 mg/kg and 0.4 mg/kg of the GPRC5DxCD3 bispecific antibody prior to subcutaneously administering a treatment dose.

29. The method of any of claims 1-28, comprising subcutaneously administering step-up doses of the GPRC5DxCD3 bispecific antibody 2-4 days apart from each other.

30. The method of any of claims 1-29 comprising orally administering the pomalidomide in an amount of 2 mg daily or 4 mg daily.

31. The method of any of claims 1-29 comprising orally administering the pomalidomide in an amount of 2 mg daily.

32. The method of any of claims 1-29 comprising orally administering the pomalidomide in an amount of 4 mg daily.

33. The method of any of claims 1-32, wherein the combination therapy comprises sequential 28-day treatment cycles.

34. The method of any of claims 1-32, wherein the pomalidomide is administered in an amount of 2 mg daily or 4 mg daily for Days 1-21 of each pomalidomide treatment cycle.

35. The method of any of claims 1-32, wherein the pomalidomide is administered in an amount of 2 mg daily for Days 1-21 of each pomalidomide treatment cycle.

36. The method of any of claims 1-32, wherein the pomalidomide is administered in an amount of 4 mg daily for Days 1-21 of each pomalidomide treatment cycle.

37. The method of any of claims 1-36, wherein:

the combination therapy comprises sequential 28-day treatment cycles;

administration of the GPRC5DxCD3 bispecific antibody starts in Cycle 1; and

administration of the pomalidomide starts in Cycle 2.

38. The method of any of claims 1-37, wherein:

the combination therapy comprises sequential 28-day treatment cycles;

Cycle 1 is a step-up phase comprising administration of one or more step-up doses and one or more treatment doses of the GPRC5DxCD3 bispecific antibody; and

each subsequent treatment cycle (Cycle 2 onward) comprises oral administration of the pomalidomide in an amount of 2 mg daily on Days 1-21; and subcutaneous administration of the GPRC5DxCD3 bispecific antibody in an amount of either (i) 0.4 mg/kg weekly (QW), or (ii) 0.8 mg/kg bi-weekly (Q2W).

39. The method of any of claims 1-38, wherein:

the combination therapy comprises sequential 28-day treatment cycles;

Cycle 1 is a step-up phase comprising administration of a first step-up dose of 0.01 mg/kg, a second step-up dose of 0.06 mg/kg, a third step-up dose of 0.4 mg/kg, and a first treatment dose of 0.8 mg/kg of the GPRC5DxCD3 bispecific antibody; and

each subsequent treatment cycle (Cycle 2 onward) comprises oral administration of the pomalidomide in an amount of 2 mg daily on Days 1-21; and subcutaneous administration of the GPRC5DxCD3 bispecific antibody in an amount of 0.8 mg/kg bi-weekly (Q2W) (e.g., on Days 1 and 15).

40. The method of any of claims 1-39, wherein the subject achieves a clinical response that is a PR, or a VGPR, or a CR or a sCR.

41. The method of any of claims 1-39, wherein the subject achieves a clinical response that is a VGPR, a CR or a sCR.

42. The method of any of claims 1-39, wherein the subject achieves a clinical response that is a CR or a sCR.

43. The method of any of claims 1-42, wherein the subject has received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, and wherein the method comprises:

treating the subject according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein:

one or more step-up doses of the GPRC5DxCD3 bispecific antibody (e.g., talquetamab) are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg,

wherein the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, regardless of clinical response in the subject, and

the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, wherein the pomalidomide may optionally

be administered in an amount of 4 mg daily (instead of 2 mg daily) on Days 1-21 of each treatment cycle, starting in treatment Cycle 3.

44. The method of any of claims 1-43, wherein the method further comprises administering dexamethasone to the subject.

45. The method of claim 44, wherein the dexamethasone is administered orally or intravenously in an amount of 40 mg (or equivalent) once per wek.

46. The method of claim 43, wherein dexamethasone is administered to the subject orally or intravenously in an amount of 40 mg (or equivalent) once per week (e.g., on Days 1, 8, 15 and 22) during treatment Cycles 2-4 only.

47. A method of improving median progression free survival (PFS) in a population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said method comprising administering to the population of subjects a combination therapy comprising a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody (e.g., talquetamab), a therapeutically effective amount of pomalidomide and a therapeutically effective amount of dexamethasone, wherein the method comprises:

treating the subject according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein:

one or more step-up doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg,

wherein the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, regardless of clinical response in the subject, and

wherein the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, wherein the pomalidomide may

optionally be administered in an amount of 4 mg daily (instead of 2 mg daily) on Days 1-21 of each treatment cycle, starting in treatment Cycle 3, and

wherein the dexamethasone is administered orally or intravenously in an amount of 40 mg (or equivalent) once per week (e.g., on Days 1, 8, 15 and 22) during treatment Cycles 2-4 only,

wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said reference population having been administered either (i) elotuzumab, pomalidomide, and dexamethasone (EPd) or (ii) pomalidomide, bortezomib, and dexamethasone (PVd).

48. A method of improving overall response rate (ORR) in a population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said method comprising administering to the population of subjects a combination therapy comprising a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody (e.g., talquetamab), a therapeutically effective amount of pomalidomide and a therapeutically effective amount of dexamethasone, wherein the method comprises:

treating the subject according to a therapeutically effective regimen that comprises sequential 28-day treatment cycles, wherein:

one or more step-up doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject during a step-up phase in Cycle 1, and then each treatment dose of the GPRC5DxCD3 bispecific antibody is subcutaneously administered to the subject in an amount of 0.8 mg/kg,

wherein the treatment doses of the GPRC5DxCD3 bispecific antibody are administered to the subject on a bi-weekly dosing schedule (Q2W) starting from treatment Cycle 2 (e.g., on Days 1 and 15), and then treatment doses of the GPRC5DxCD3 bispecific antibody are subcutaneously administered to the subject on a monthly dosing schedule (Q4W) either: (i) starting at treatment Cycle 5 if the subject has achieved a very good partial response, a complete response or a stringent complete response, as determined by IMWG response criteria; or (ii) starting at treatment Cycle 7, regardless of clinical response in the subject, and

wherein the pomalidomide is orally administered in an amount of 2 mg daily on Days 1-21 of each treatment cycle, starting in treatment Cycle 2, wherein the pomalidomide may optionally be administered in an amount of 4 mg daily (instead of 2 mg daily) on Days 1-21 of each treatment cycle, starting in treatment Cycle 3, and

wherein the dexamethasone is administered orally or intravenously in an amount of 40 mg (or equivalent) once per week (e.g., on Days 1, 8, 15 and 22) during treatment Cycles 2-4 only,

wherein the improvement in ORR is relative to ORR of a reference population of subjects with relapsed or refractory multiple myeloma that have received between 1-4 prior lines of therapy including an anti-CD38 antibody (e.g., daratumumab) and lenalidomide, said reference population having been administered either (i) elotuzumab, pomalidomide, and dexamethasone (EPd) or (ii) pomalidomide, bortezomib, and dexamethasone (PVd).

49. The method of any of claims 43-48, wherein the step-up phase comprises subcutaneously administering step-up doses of 0.01 mg/kg and 0.06 mg/kg of the GPRC5DxCD3 bispecific antibody 2-4 days apart from each other (e.g., on Days 1 and 4, respectively).

50. The method of any of claims 43-48, wherein the step-up phase comprises subcutaneously administering step-up doses of 0.01 mg/kg, 0.06 mg/kg and 0.4 mg/kg of the GPRC5DxCD3 bispecific antibody 2-4 days apart from each other (e.g., on Days 1, 4 and 8, respectively).

51. The method of any of claims 43-48, wherein the step-up phase comprises subcutaneously administering step-up doses of 0.01 mg/kg, 0.06 mg/kg and 0.4 mg/kg of the GPRC5DxCD3 bispecific antibody 2-4 days apart from each other (e.g., on Days 1, 4 and 8, respectively) and then subcutaneously administering the treatment dose of 0.8 mg/kg of the GPRC5DxCD3 bispecific antibody at least two days after the 0.4 mg/kg dose (e.g., between Days 7-15, such as Day 15).

Fig. 1: MonumenTAL-2 Phase 1b study design

[a]For talquetamab + pomalidomide cohort. [b]AEs assessed per CTCAE v5.0, except for CRS and ICANS, which were graded per ASTCT guidelines. [c]Assessed per IMWG 2016 criteria. AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; BsAb, bispecific antibody; CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GPRC5D, G protein–coupled receptor family C group 5 member D; ICANS, immune effector cell–associated neurotoxicity syndrome; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; ORR, overall response rate; PFS, progression-free survival; PI, proteasome inhibitor; PO, by mouth; QW, weekly; Q2W, every other week; SC, subcutaneous.

Fig. 2: MonumenTAL-2 (Tal + Pom) patient characteristics

Characteristic	Tal 0.4 mg/kg QW + pom (n=16)	Tal 0.8 mg/kg Q2W + pom (n=19)
Age (years), median (range)	69.5 (49–78)	63.0 (43–76)
Male, n (%)	7 (43.8)	14 (73.7)
Race, n (%)		
White	12 (75.0)	16 (84.2)
African American/Black	1 (6.3)	2 (10.5)
Unknown/not reported	3 (18.8)	1 (5.3)
Extramedullary plasmacytomas ≥1, n (%)[a]	2 (12.5)	3 (15.8)
High-risk cytogenetics,[b] n (%)	5 (31.3)	4 (21.1)
ISS stage, n (%)		
I	5 (31.3)	6 (31.6)
II	9 (56.3)	10 (52.6)
III	2 (12.5)	3 (15.8)

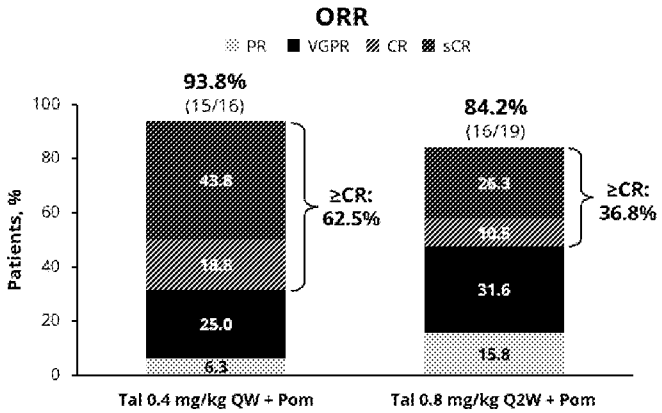
Characteristic	Tal 0.4 mg/kg QW + pom (n=16)	Tal 0.8 mg/kg Q2W + pom (n=19)
Time since diagnosis (months), median (range)	71.8 (16.9–153.9)	49.7 (18.7–166.8)
Prior lines of therapy, median (range)	3 (2–12)	3 (2–5)
Exposure status, n (%)		
Triple-class	12 (75.0)	14 (73.7)
Penta-drug	5 (31.3)	3 (15.8)
Anti-BCMA BsAb	1 (6.3)	0
Anti-BCMA CAR-T therapy	3 (18.8)	0
Pomalidomide	5 (31.3)	3 (15.8)
Anti-CD38 antibody	12 (75.0)	14 (73.7)
Refractory status, n (%)		
Triple-class	5 (31.3)	4 (21.1)
Penta-drug	1 (6.3)	0
Pomalidomide	4 (25.0)	1 (5.3)
Anti-CD38 antibody	12 (75.0)	7 (36.8)
Last line of prior therapy	8 (50.0)	10 (52.6)

Data cut-off date: October 11, 2023.

[a]Clinical examination or magnetic resonance imaging was used to document extramedullary sites of disease. [b]del(17p), t(4;14), and/or t(14;16).

BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CAR-T, chimeric antigen receptor T cell; ISS, International Staging System; pom, pomalidomide; Q2W, every other week; QW, weekly; tal, talquetamab.

Fig. 3: MonumenTAL-2 (Tal + Pom): High ORR with rapid and deep responses



	Tal 0.4 mg/kg QW + pom (n=16)	Tal 0.8 mg/kg Q2W + pom (n=19)
Median follow-up, months (range)	15.0 (1.2–19.0)	11.1 (1.2–14.8)
Median time to first response, months (range)	1.7 (0.9–3.3)	1.2 (0–4.8)

Data cut-off date: October 11, 2023.
CAR-T, chimeric antigen receptor T cell; CR, complete response; EMD, extramedullary disease; NR, not reached; ORR, overall response rate; pom, pomalidomide; PR, partial response; Q2W, every other week;
QW, weekly; sCR, stringent complete response; tal, talquetamab; VGPR, very good partial response.

FIG. 4: Schematic Overview of MonumenTAL-6 Clinical Study

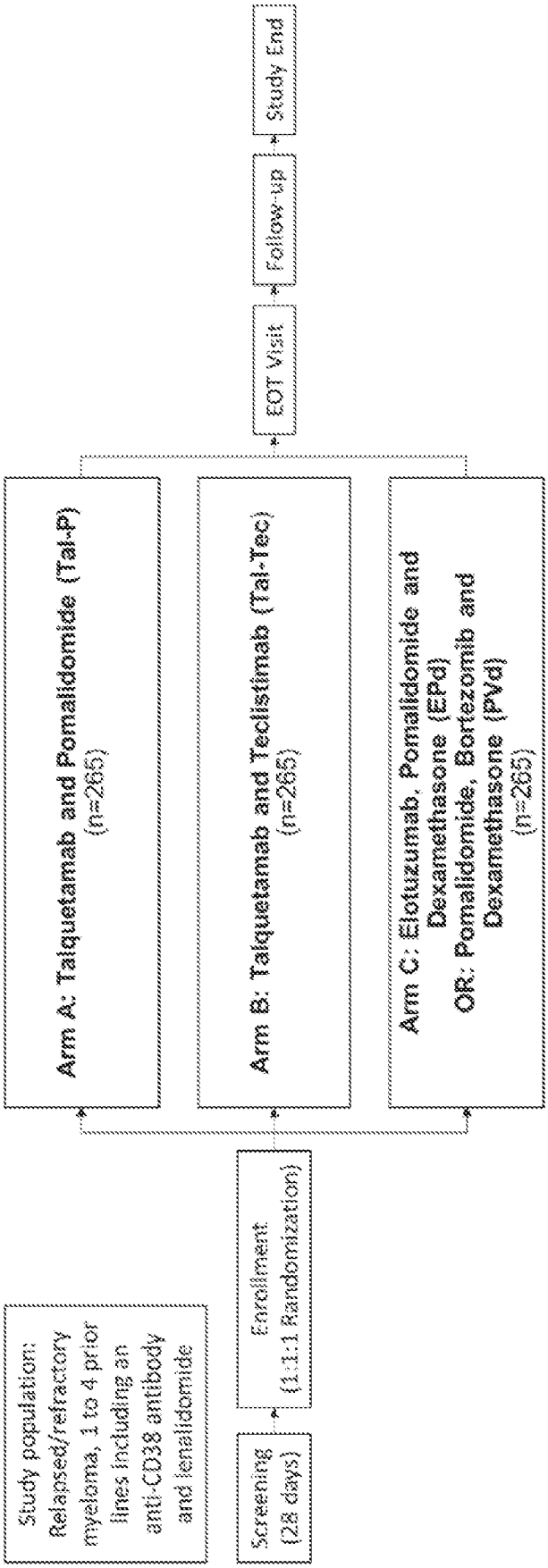


FIG. 5a: Dosing Schedule for Pretreatment Medications in Arm A (Tal-Pom) of MonumenTAL-6

Cycle	Notes	Treatment Phase (28-day cycle)						
		Cycle 1				Cycle 2-6		Cycle 7+
Day		1	4	8	15	1 ±3d	15 ±3d	1 ±3d
Dexamethasone 20 mg or equivalent (see Appendix 13)	• PO/IV: administer 1–3 h (±15 mins) prior to talquetamab SC/teclistamab SC • Prior to all step-up doses and first treatment dose in C1	X	X	X	X			
Diphenhydramine 25 to 50 mg, or equivalent		X	X	X	X			
Acetaminophen 650 to 1000 mg		X	X	X	X			

FIG. 5b: Initial Dosing Schedule for Study Treatments in Arm A (Tal-Pom) of MonumenTAL-6

Cycle	Notes	Treatment Phase (28-day cycle)						
		Cycle 1				Cycle 2-6		Cycle 7+
Day		1	4	8	15	1 ±3d	15 ±3d	1 ±3d
Talquetamab SC SU1 (0.01 mg/kg)[b,c]		X						
Talquetamab SC SU2 (0.06 mg/kg)[b,c]	• Administer ≥2d after SU1, between Days 3-6		X					
Talquetamab SC Treatment Dose (0.4 mg/kg)[b,c]	• Administer ≥2d after SU2, between Days 5-10			X				
Talquetamab SC Treatment Dose (0.8 mg/kg)[b,c]	• Administer ≥2d after first treatment dose, between Days 7-15 • C2-C4 talquetamab SC must be administered 14d (±3d) after prior treatment dose • From C5, if confirmed VGPR or better, schedule can change to Q4W dosing (D1 only) per investigator discretion • Q4W from C7 for all participants				X	X	X	X[d]
Dexamethasone 40 mg or equivalent (Arm A [Tal-P] only)	• Administered weekly (Days 1, 8, 15, and 22) during C2-C4 only • For participants <75 years of age with BMI <18.5 or ≥75 years of age, the weekly dose of dexamethasone is 20 mg					X	X	
Pomalidomide[e] (Arm A [Tal-P] only)	• Administer ≥7d between the course of pomalidomide treatment for each cycle					Days 1-21[e]		Days 1-21[e]

e. Pomalidomide (Arm A [Tal-P] only) will be initiated at 2 mg daily at C2D1, and may be increased to 4 mg daily per investigator discretion from C3D1. The selected dose regimen for pomalidomide is based on standard doses used in clinical practice for the treatment of multiple myeloma, as detailed in respective product information.

FIG. 5c: Updated Dosing Schedule for Study Treatments in Arm A (Tal-Pom) of MonumenTAL-6

Cycle / Day	Notes	Treatment Phase (28-day cycle)						
		Cycle 1				Cycle 2-6		Cycle 7+
		1	4	8	15	1 ±3d	15 ±3d	1 ±3d
Talquetamab SC SU1 (0.01 mg/kg)[b,c]		X						
Talquetamab SC SU2 (0.06 mg/kg)[b,c]	• Administer ≥2d after SU1		X					
Talquetamab SC Treatment Dose (0.4 mg/kg)[b,c]	• Administer ≥2d after SU2			X				
Talquetamab SC Study Treatment Dose (0.8 mg/kg)[b,c]	• Administer ≥2d after first study treatment dose, between Days 7-15 • C2-C4 talquetamab SC must be administered 14d (±3d) after prior treatment dose *From C5, if confirmed VGPR or better, schedule can change to Q4W dosing (D1 only) per investigator discretion Change to Q4W dosing should occur on C5 or C6 Day 1 (±3d) #At C7 Day 1 (±3d), participants with response of confirmed PR or better must change to Q4W dosing. In exceptional cases only, participants can continue Q2W dosing after sponsor consultation and approval. For all participants who are not in confirmed PR or better at C7D1, continue with Q2W dosing until confirmed PR or better is achieved.				X	X	X*	X*#
Dexamethasone 40 mg or equivalent	• Administered weekly (Days 1, 8, 15, and 22) during C2-C4 only • For participants <75 years of age with BMI <18.5 or ≥75 years of age, the weekly dose of dexamethasone is 20 mg					X	X	
Pomalidomide[e]	• Administer ≥7d between the course of pomalidomide treatment for each cycle					Days 1-21*		Days 1-21*

d. Participants will receive therapy with talquetamab/teclistamab (as appropriate) for up to 26 cycles if they have no sign of PD or toxicity. Participants can continue therapy w pomalidomide (Arm A [Tal-P] only) beyond Cycle 26 if no discontinuation criteria are met.

e. Pomalidomide (Arm A [Tal-P] only) will be initiated at 2 mg daily at C2D1, and may be increased to 4 mg daily per investigator discretion from C3D1. The selected dose regimen forpomalidomide is based on standard doses used in clinical practice for the treatment of multiple myeloma.

FIG. 6a: Dosing Schedule for Pretreatment Medications in Arm C (EPd) of MonumenTAL-6

Cycle	Notes	Treatment Phase (28-day cycle)											
		Cycle 1				Cycle 2				Cycle 3+			
Day		1	8	15	22	1	8	15	22	1	8	15	22
Acetaminophen 650 to 1000 mg PO	* Administer 45–90 min before elotuzumab	X	X	X	X	X	X	X	X	X			
Diphenhydramine (25 to 50 mg IV or PO) or equivalent		X	X	X	X	X	X	X	X	X			
Ranitidine (50 mg IV) or equivalent		X	X	X	X	X	X	X	X	X			
Dexamethasone 8 mg IV/PO		X	X	X	X	X	X	X	X	X			

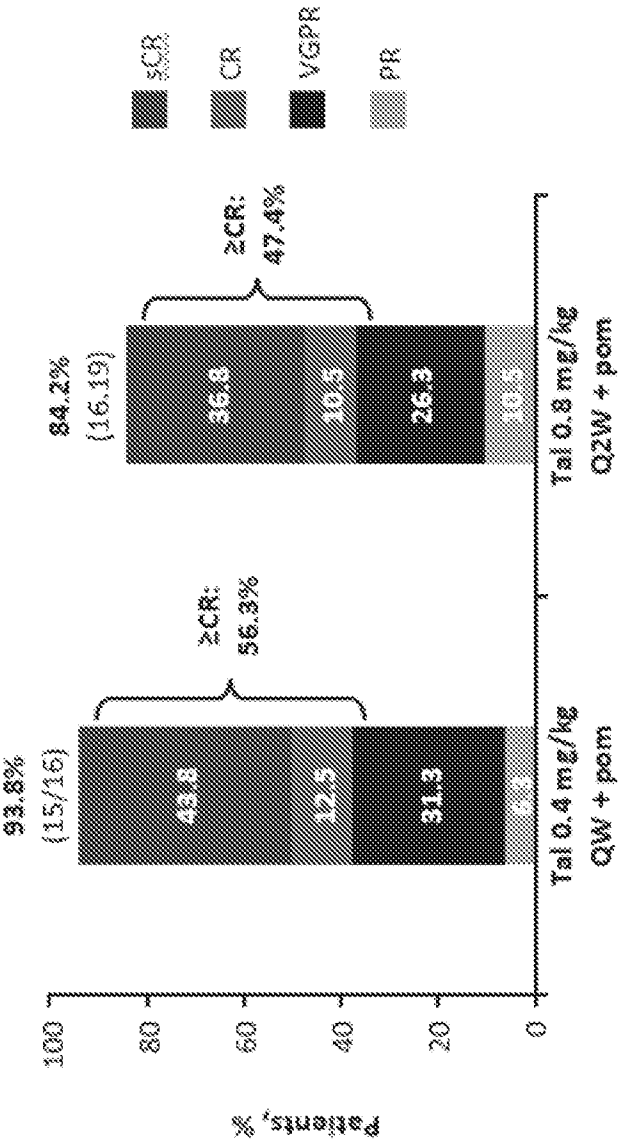
FIG. 6b: Dosing Schedule for Study Treatments in Arm C (EPd) of MonumenTAL-6

Cycle	Notes	Treatment Phase (28-day cycle)											
		Cycle 1				Cycle 2				Cycle 3+			
Day		1	8	15	22	1	8	15	22	1	8	15	22
Elotuzumab IV	10 mg/kg for Cycles 1 and 2, and 20 mg/kg for Cycles 3+	X	X	X	X	X	X	X	X	X			
Pomalidomide PO	4 mg/day There must be ≥7d between the course of pomalidomide for each cycle	Days 1-21				Days 1-21				Days 1-21			
Dexamethasone PO	≤75 years of age (between 3-24 h before elotuzumab)	28mg	28mg	28mg	28mg	28mg	28mg	28mg	28mg	28mg	40mg	40mg	40mg
Dexamethasone PO	>75 years of age (between 3-24 h before elotuzumab)	12mg	12mg	12mg	12mg	12mg	12mg	12mg	12mg	12mg	20mg	20mg	20mg

FIG. 6c: Dosing Schedule for Study Treatments in Arm C (PVd) of MonumenTAL-6

								Treatment Phase (21-day cycle)											
								Cycle 1-8								Cycle 9+			
								1	2	3	4	5	6	9	11	13	1	2	3	4
Day																				
Pomalidomide PO	4 mg/day There must be ≥7d between the course of pomalidomide for each cycle							Days 1-14									Days 1-14			
Bortezomib SC	1.3 mg/m² There must be ≥3d between doses of bortezomib							X			X		X		X		X		X	
Dexamethasone PO	20 mg/day (≤75 years of age) or 10 mg/day (>75 years of age)							X	X		X	X	X	X	X	X	X	X	X	X

FIG. 7: Overall Response Rate from the Ph1b MonumenTAL-2 Study (April 22, 2024 data cutoff)



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/060718

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61P35/00 A61K31/454 C07K16/28 A61K39/00 A61K39/395
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61P A61K C07K

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VERKLEIJ CHRISTIE P. M. ET AL: "Preclinical activity and determinants of response of the GPRC5DxCD3 bispecific antibody talquetamab in multiple myeloma", BLOOD ADVANCES, vol. 5, no. 8, 27 April 2021 (2021-04-27), pages 2196-2215, XP055880142, ISSN: 2473-9529, DOI: 10.1182/bloodadvances.2020003805 abstract ----- -/--	1-51

[X] Further documents are listed in the continuation of Box C.

[ ] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 March 2025	10/04/2025

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Turri, Matteo

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/060718

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Anonymous: "Record History ¦ ver. 29: 2023-10-10 ¦ NCT05050097 ¦ ClinicalTrials.gov", , 11 October 2023 (2023-10-11), XP093249550, Retrieved from the Internet: URL:https://clinicaltrials.gov/study/NCT05050097?tab=history&a=29#version-content-panel the whole document -----	1-51
A	CHARI AJAI ET AL: "Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma", THE NEW ENGLAND JOURNAL OF MEDICINE, vol. 387, no. 24, 15 December 2022 (2022-12-15), pages 2232-2244, XP093183744, US ISSN: 0028-4793, DOI: 10.1056/NEJMoa2204591 abstract -----	1-51
A	SCHINKE CAROLINA D. ET AL: "Pivotal phase 2 MonumenTAL-1 results of talquetamab (tal), a GPRC5DxCD3 bispecific antibody (BsAb), for relapsed/refractory multiple myeloma (RRMM).", JOURNAL OF CLINICAL ONCOLOGY, vol. 41, no. 16_suppl, 1 June 2023 (2023-06-01), pages 8036-8036, XP093259773, ISSN: 0732-183X, DOI: 10.1200/JCO.2023.41.16_suppl.8036 the whole document -----	1-51
X,P	MATOUS JEFFREY ET AL: "Talquetamab + Pomalidomide in Patients with Relapsed/Refractory Multiple Myeloma: Safety and Preliminary Efficacy Results from the Phase 1b MonumenTAL-2 Study", BLOOD, vol. 142, no. Supplement 1, 2 November 2023 (2023-11-02), pages 1014-1014, XP093249553, AMSTERDAM, NL ISSN: 0006-4971, DOI: 10.1182/blood-2023-187706 the whole document -----	1-15

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/060718

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZANDER THILO ET AL: "Alternate-day dosing of pomalidomide in relapsed/ refractory multiple myeloma: a multicenter, single-arm phase 2 trial", BLOOD CANCER JOURNAL, vol. 37, no. 3, 12 January 2023 (2023-01-12), pages 699-701, XP093259807, London ISSN: 0887-6924, DOI: 10.1038/s41375-023-01809-z Retrieved from the Internet: URL:https://www.nature.com/articles/s41375-023-01809-z> -----	1-51

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2024/060718

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

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed.

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments: