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(54) **DOSING FOR TREATMENT WITH ANTI-FCRH5/ANTI-CD3 BISPECIFIC ANTIBODIES**

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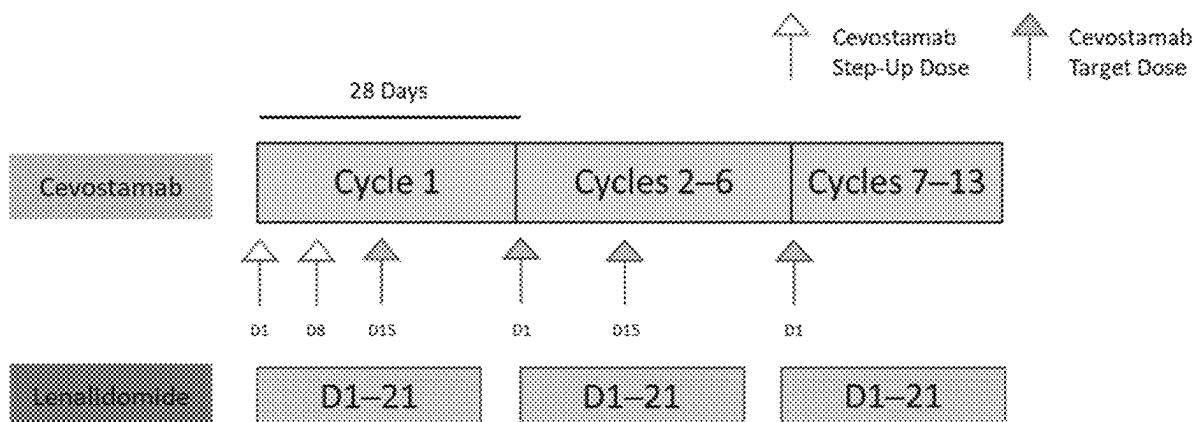
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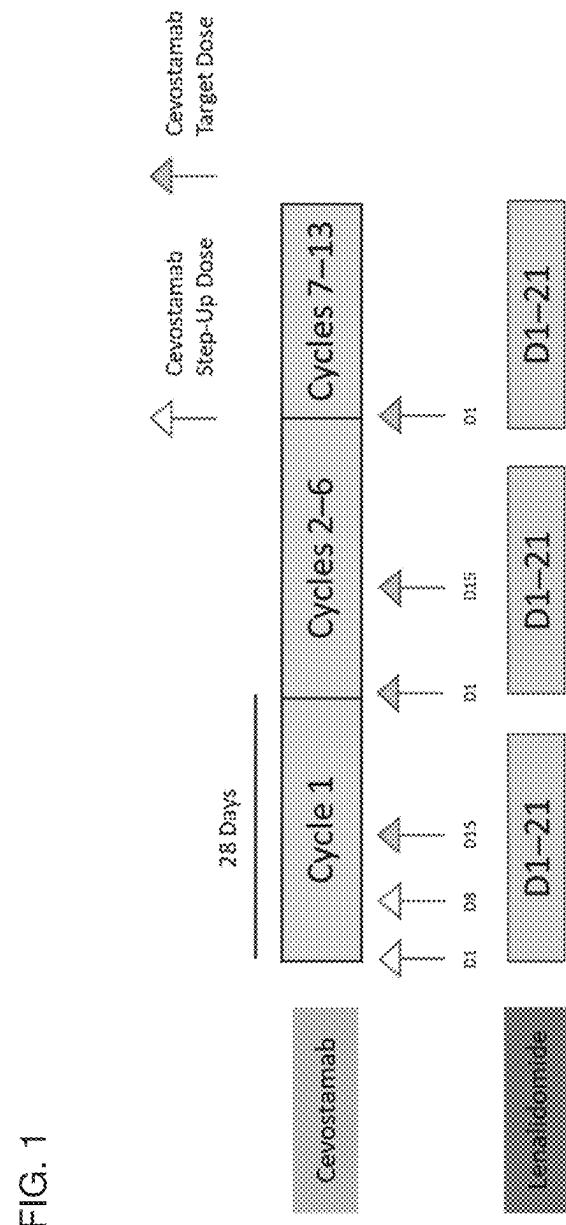
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ABSTRACT

The invention provides methods of dosing for the treatment of cancers, such as multiple myelomas, with anti-fragment crystallizable receptor-like 5 (FcRH5)/anti-cluster of differentiation 3 (CD3) bispecific antibodies and lenalidomide.

Specification includes a Sequence Listing.





DOSING FOR TREATMENT WITH ANTI-FCRH5/ANTI-CD3 BISPECIFIC ANTIBODIES

SEQUENCE LISTING

[0001] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on Jan. 15, 2025, is named 50474-302004_Sequence_Listing_1_15_25_. XML and is 41,595 bytes in size.

FIELD OF THE INVENTION

[0002] The present invention relates to the treatment of cancers, such as B cell proliferative disorders. More specifically, the invention concerns the specific treatment of human patients having multiple myeloma (MM) using an anti-fragment crystallizable receptor-like 5 (FcRH5)/anti-cluster of differentiation 3 (CD3) bispecific antibody and lenalidomide.

BACKGROUND

[0003] Cancer remains one of the deadliest threats to human health. In the U.S., cancer affects more than 1.7 million new patients each year and is the second leading cause of death after heart disease, accounting for approximately one in four deaths.

[0004] Hematologic cancers, in particular, are the second leading cause of cancer-related deaths. Hematologic cancers include multiple myeloma (MM), a neoplasm characterized by the proliferation and accumulation of malignant plasma cells. Worldwide, approximately 110,000 people are diagnosed with MM annually. MM remains incurable despite advances in treatment, with an estimated median survival of 8-10 years for standard-risk myeloma and 2-3 years for high-risk disease, despite receipt of an autologous stem cell transplant (ASCT). Despite the significant improvement in patient's survival over the past 20 years, only 10-15% of patients achieve or exceed expected survival compared with the matched general population.

[0005] Therefore, there is a need for improved treatment regimens for MM and other hematologic cancers.

SUMMARY OF THE INVENTION

[0006] Provided herein are, inter alia, methods of treating a subject having a cancer (e.g., MM), compositions for use, and related articles of manufacture.

[0007] In one aspect, provided herein is a method of treating a subject having a multiple myeloma (MM) with a high-risk cytogenetic feature, the method comprising administering to the subject (i) a bispecific antibody that binds to fragment crystallizable receptor-like 5 (FcRH5) and cluster of differentiation 3 (CD3) and (ii) lenalidomide.

[0008] In another aspect, provided herein is a bispecific antibody that binds to FcRH5 and CD3 for use in treatment of a subject having an MM with high-risk cytogenetic features, the treatment comprising administration of the bispecific antibody and lenalidomide to the subject.

[0009] In some aspects, the subject has experienced a partial response (PR) or better after induction therapy.

[0010] In some aspects, the subject has undergone autologous stem cell transplantation (ASCT) within 100 days of the onset of the method or treatment and/or has an absence of progressive disease.

[0011] In some aspects, the bispecific antibody and lenalidomide are administered to the patient as a post-transplant maintenance therapy.

[0012] In some aspects, the high-risk cytogenetic feature comprises one or more of the following: translocation events t(4;14) or t(14;16), del(17p), or 1q gain.

[0013] In some aspects, the subject harbored the high-risk cytogenetic feature at the time of diagnosis of MM.

[0014] In some aspects, the bispecific antibody and the lenalidomide are administered to the subject in a dosing regimen comprising: (i) a first phase comprising one or more dosing cycles, wherein the first phase comprises administering the bispecific antibody to the subject every two weeks (Q2W); (ii) a second phase comprising one or more dosing cycles, wherein the second phase comprises administering the bispecific antibody to the subject every four weeks (Q4W).

[0015] In some aspects, each dosing cycle of the first phase and/or the second phase is a 28-day dosing cycle.

[0016] In some aspects, the method or treatment further comprising a pre-phase, prior to the first phase, comprising one or more dosing cycles, wherein the pre-phase comprises administering the bispecific antibody to the subject every week (QW).

[0017] In some aspects, each dosing cycle of the pre-phase is a 28-day dosing cycle.

[0018] In some aspects, the pre-phase comprises one dosing cycle (C1).

[0019] In some aspects, the pre-phase comprises administering the bispecific antibody to the subject on Days 1, 8, and 15 of the C1.

[0020] In some aspects, a target dose of the bispecific antibody is administered to the subject for each administration in the pre-phase.

[0021] In some aspects, the pre-phase comprises administering a first step-up dose of the bispecific antibody to the subject.

[0022] In some aspects, the first step-up dose is administered to the subject on Day 1 of the C1.

[0023] In some aspects, a target dose is administered to the subject on Days 8 and 15 of the C1.

[0024] In some aspects, the pre-phase comprises administering a first step-up dose and a second step-up dose of the bispecific antibody to the subject.

[0025] In some aspects, the first step-up dose is administered to the subject on Day 1 of C1 and the second step-up dose is administered to the subject on Day 8 of the C1.

[0026] In some aspects, a target dose is administered to the subject on Day 15 of the C1.

[0027] In some aspects, the first step-up dose is 3.6 mg.

[0028] In some aspects, the first step-up dose is 0.3 mg and the second step-up dose is 3.6 mg.

[0029] In some aspects, the first phase comprises at least two dosing cycles, at least three dosing cycles, at least four dosing cycles, or at least five dosing cycles.

[0030] In some aspects, the first phase comprises a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), and a fifth dosing cycle (C5).

- [0031] In some aspects, the first phase comprises administering the bispecific antibody to the subject on Days 1 and 15 of the C1, the C2, the C3, the C4, and/or the C5.
- [0032] In some aspects, a target dose of the bispecific antibody is administered to the subject for each administration during the first phase.
- [0033] In some aspects, the second phase comprises at least two dosing cycles, at least three dosing cycles, at least four dosing cycles, at least five dosing cycles, at least six dosing cycles, or at least seven dosing cycles.
- [0034] In some aspects, the second phase comprises a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), a fifth dosing cycle (C5), a sixth dosing cycle (C6), and a seventh dosing cycle (C7).
- [0035] In some aspects, the second phase comprises administering the bispecific antibody to the subject on Day 1 of the C1, the C2, the C3, the C4, the C5, the C6, and/or the C7.
- [0036] In some aspects, a target dose of the bispecific antibody is administered to the subject for each administration during the second phase.
- [0037] In some aspects, the target dose is between 90 mg to 198 mg, inclusive.
- [0038] In some aspects, the target dose is 90 mg.
- [0039] In some aspects, the target dose is 132 mg.
- [0040] In some aspects, the target dose is 160 mg.
- [0041] In some aspects, the bispecific antibody is administered to the subject intravenously.
- [0042] In some aspects, the lenalidomide is administered to the subject on Days 1-21 of each dosing cycle in the first phase and/or the second phase.
- [0043] In some aspects, the lenalidomide is administered to the subject on Days 1-21 of each dosing cycle in the pre-phase.
- [0044] In some aspects, the lenalidomide is administered to the subject at a dosage of about 10 mg to about 20 mg.
- [0045] In some aspects, the lenalidomide is administered to the subject at a dosage of about 10 mg.
- [0046] In some aspects, the lenalidomide is administered to the subject at a dosage of about 15 mg.
- [0047] In some aspects, the lenalidomide is administered to the subject orally.
- [0048] In some aspects, the method or treatment further comprises administering a corticosteroid to the subject.
- [0049] In some aspects, the method or treatment further comprises administering a corticosteroid to the subject during the first phase and/or the second phase.
- [0050] In some aspects, the corticosteroid is administered to the subject during the first phase on Days 1 and 15 of the C1 of the first phase.
- [0051] In some aspects, the corticosteroid is administered to the subject in the C2, the C3, the C4, and/or the C5 of the first phase if the subject experienced a cytokine release syndrome (CRS) event with the prior dose.
- [0052] In some aspects, the corticosteroid is administered to the subject in the C1, the C2, the C3, the C4, the C5, the C6, and/or the C7 of the second phase if the subject experienced a CRS event with the prior dose.
- [0053] In some aspects, the method or treatment further comprises administering a corticosteroid to the subject during the pre-phase.
- [0054] In some aspects, the corticosteroid is administered to the subject during the pre-phase on Days 1, 8, and 15 of the C1.
- [0055] In some aspects, the corticosteroid is administered to the subject intravenously or orally.
- [0056] In some aspects, the corticosteroid is administered to the subject intravenously.
- [0057] In some aspects, the corticosteroid is administered to the subject intravenously prior to the administration of the bispecific antibody.
- [0058] In some aspects, the corticosteroid is administered to the subject intravenously about 1 hour prior to the administration of the bispecific antibody.
- [0059] In some aspects, the corticosteroid is dexamethasone or methylprednisolone.
- [0060] In some aspects, the corticosteroid is dexamethasone.
- [0061] In some aspects, the dexamethasone is administered to the subject at a dosage of about 20 mg.
- [0062] In some aspects, the methylprednisolone is administered to the subject at a dosage of about 80 mg.
- [0063] In some aspects, the bispecific antibody comprises an anti-FcRH5 arm comprising a first binding domain comprising the following six hypervariable regions (HVRs): (a) an HVR-H1 comprising the amino acid sequence of RFGVH (SEQ ID NO: 1); (b) an HVR-H2 comprising the amino acid sequence of VIWRGGSTDYNAAFVS (SEQ ID NO: 2); (c) an HVR-H3 comprising the amino acid sequence of HYYGSSDYALDN (SEQ ID NO: 3); (d) an HVR-L1 comprising the amino acid sequence of KASQDVRNLVV (SEQ ID NO: 4); (e) an HVR-L2 comprising the amino acid sequence of SGSYRYS (SEQ ID NO: 5); and (f) an HVR-L3 comprising the amino acid sequence of QQHYSPPYT (SEQ ID NO: 6).
- [0064] In some aspects, the bispecific antibody comprises an anti-FcRH5 arm comprising a first binding domain comprising (a) a heavy chain variable (VH) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 7; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 8; or (c) a VH domain as in (a) and a VL domain as in (b).
- [0065] In some aspects, the first binding domain comprises a VH domain comprising an amino acid sequence of SEQ ID NO: 7 and a VL domain comprising an amino acid sequence of SEQ ID NO: 8.
- [0066] In some aspects, the bispecific antibody comprises an anti-CD3 arm comprising a second binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SYYIH (SEQ ID NO: 9); (b) an HVR-H2 comprising the amino acid sequence of WIYPENDNTKYNEKFKD (SEQ ID NO: 10); (c) an HVR-H3 comprising the amino acid sequence of DGYSRYYFDY (SEQ ID NO: 11); (d) an HVR-L1 comprising the amino acid sequence of KSSQSLLNSRTRKNYLA (SEQ ID NO: 12); (e) an HVR-L2 comprising the amino acid sequence of WTSTRKS (SEQ ID NO: 13); and (f) an HVR-L3 comprising the amino acid sequence of KQSFILRT (SEQ ID NO: 14).
- [0067] In some aspects, the bispecific antibody comprises an anti-CD3 arm comprising a second binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino

acid sequence of SEQ ID NO: 15; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 16; or (c) a VH domain as in (a) and a VL domain as in (b).

[0068] In some aspects, the second binding domain comprises a VH domain comprising an amino acid sequence of SEQ ID NO: 15 and a VL domain comprising an amino acid sequence of SEQ ID NO: 16.

[0069] In some aspects, the bispecific antibody comprises an anti-FcRH5 arm comprising a heavy chain polypeptide (H1) and a light chain polypeptide (L1) and an anti-CD3 arm comprising a heavy chain polypeptide (H2) and a light chain polypeptide (L2), and wherein: (a) H1 comprises the amino acid sequence of SEQ ID NO: 35; (b) L1 comprises the amino acid sequence of SEQ ID NO: 36; (c) H2 comprises the amino acid sequence of SEQ ID NO: 37; and (d) L2 comprises the amino acid sequence of SEQ ID NO: 38.

[0070] In some aspects, the bispecific antibody comprises an aglycosylation site mutation.

[0071] In some aspects, the aglycosylation site mutation reduces effector function of the bispecific antibody.

[0072] In some aspects, the aglycosylation site mutation is a substitution mutation.

[0073] In some aspects, the bispecific antibody comprises a substitution mutation in the Fc region that reduces effector function.

[0074] In some aspects, the bispecific antibody is a monoclonal antibody.

[0075] In some aspects, the bispecific antibody is a humanized antibody.

[0076] In some aspects, the bispecific antibody is a chimeric antibody.

[0077] In some aspects, the bispecific antibody is an antibody fragment that binds FcRH5 and CD3.

[0078] In some aspects, the antibody fragment is selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.

[0079] In some aspects, the bispecific antibody is a full-length antibody.

[0080] In some aspects, the bispecific antibody is an IgG antibody.

[0081] In some aspects, the IgG antibody is an IgG₁ antibody.

[0082] In some aspects, the bispecific antibody comprises one or more heavy chain constant domains, wherein the one or more heavy chain constant domains are selected from a first CH1 (CH1₁) domain, a first CH2 (CH2₁) domain, a first CH3 (CH3₁) domain, a second CH1 (CH1₂) domain, second CH2 (CH2₂) domain, and a second CH3 (CH3₂) domain.

[0083] In some aspects, at least one of the one or more heavy chain constant domains is paired with another heavy chain constant domain.

[0084] In some aspects, the CH3₁ and CH3₂ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the CH3₁ domain is positionable in the cavity or protuberance, respectively, in the CH3₂ domain.

[0085] In some aspects, the CH3₁ and CH3₂ domains meet at an interface between the protuberance and cavity.

[0086] In some aspects, the CH2₁ and CH2₂ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the CH2₁ domain is positionable in the cavity or protuberance, respectively, in the CH2₂ domain.

[0087] In some aspects, the CH2₁ and CH2₂ domains meet at an interface between said protuberance and cavity.

[0088] In some aspects, the anti-FcRH5 arm comprises the protuberance and the anti-CD3 arm comprises the cavity.

[0089] In some aspects, a CH3 domain of the anti-FcRH5 arm comprises a protuberance comprising a T366W amino acid substitution mutation (EU numbering) and a CH3 domain of the anti-CD3 arm comprises a cavity comprising T366S, L368A, and Y407V amino acid substitution mutations (EU numbering).

[0090] In some aspects, the bispecific antibody is cevostamab.

[0091] In some aspects, the bispecific antibody and the lenalidomide are administered to the subject concurrently with one or more additional therapeutic agents.

[0092] In some aspects, the bispecific antibody and/or the lenalidomide are administered to the subject prior to the administration of one or more additional therapeutic agents.

[0093] In some aspects, the bispecific antibody and/or the lenalidomide is administered to the subject subsequent to the administration of one or more additional therapeutic agents.

[0094] In some aspects, the one or more additional therapeutic agents comprise an effective amount of tocilizumab.

[0095] In some aspects, the subject has a CRS event, and the method further comprises treating the symptoms of the CRS event while suspending treatment with the bispecific antibody.

[0096] In some aspects, the method or treatment further comprises administering to the subject an effective amount of tocilizumab to treat the CRS event.

[0097] In some aspects, the CRS event does not resolve or worsens within 24 hours of treating the symptoms of the CRS event, the method further comprising administering to the subject one or more additional doses of tocilizumab to manage the CRS event.

[0098] In some aspects, tocilizumab is administered to the subject by intravenous infusion.

[0099] In some aspects: (a) the subject weighs ≥30 kg, and tocilizumab is administered to the subject at a dose of 8 mg/kg; or (b) the subject weighs <30 kg, and tocilizumab is administered to the subject at a dose of 12 mg/kg.

[0100] In some aspects, tocilizumab is administered to the subject 2 hours before administration of the bispecific antibody.

[0101] In some aspects, the one or more additional therapeutic agents comprise an effective amount of a B-cell maturation antigen (BCMA)-directed therapy, an additional immunomodulator (IMID), a CD38-directed therapy, or a combination of any of the foregoing.

[0102] In some aspects, the one or more additional therapeutic agents comprise an effective amount of acetaminophen or paracetamol.

[0103] In some aspects, acetaminophen or paracetamol is administered to the subject at a dose of between about 500 mg to about 1000 mg.

[0104] In some aspects, acetaminophen or paracetamol is administered to the subject orally.

[0105] In some aspects, the one or more additional therapeutic agents comprise an effective amount of diphenhydramine.

[0106] In some aspects, diphenhydramine is administered to the subject at a dose of between about 25 mg to about 50 mg.

[0107] In some aspects, diphenhydramine is administered orally to the subject.

[0108] In another aspect, provided herein is a method of treating a subject having an MM with a high-risk cytogenetic feature, the method comprising administering to the subject cevostamab and lenalidomide, wherein: (i) the subject experienced a PR or better after induction therapy; (ii) the subject has undergone ASCT within 100 days of the onset of the method and/or has an absence of progressive disease; (iii) the cevostamab and lenalidomide are administered to the patient as a post-transplant maintenance therapy; and (iv) the high-risk cytogenetic feature comprises one or more of the following: translocation events t(4;14) or t(14;16), del(17p), or 1q gain.

[0109] In another aspect, provided herein is cevostamab for use in treatment of a subject having an MM with a high-risk cytogenetic feature, the treatment comprising administration of cevostamab and lenalidomide to the subject, wherein: (i) the subject experienced a PR or better after induction therapy; (ii) the subject has undergone ASCT within 100 days of the onset of the method and/or has an absence of progressive disease; (iii) the cevostamab and lenalidomide are administered to the patient as a post-transplant maintenance therapy; and (iv) the high-risk cytogenetic feature comprises one or more of the following: translocation events t(4;14) or t(14;16), del(17p), or 1q gain.

[0110] In another aspect, provided herein is a method of treating a subject having an MM with a high-risk cytogenetic feature, the method comprising administering to the subject cevostamab and lenalidomide in a dosing regimen comprising: (i) a pre-phase comprising a 28-day dosing cycle (C1); (ii) a first phase, following the pre-phase, comprising a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), and a fifth dosing cycle (C5), wherein each dosing cycle of the first phase is a 28-day dosing cycle; and (iii) a second phase, following the first phase, comprising a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), a fifth dosing cycle (C5), a sixth dosing cycle (C6), and a seventh dosing cycle (C7), wherein each dosing cycle of the second phase is a 28-day dosing cycle, wherein cevostamab is administered to the subject: (i) at a first step-up dose during the pre-phase on Day 1 of the C1 and as a second step-up dose during the pre-phase on Day 8 of the C1; (ii) at a target dose during the pre-phase on Day 15 of the C1; (iii) at a target dose during the first phase on Days 1 and 15 of the C1, the C2, the C3, the C4, and the C5; and (iv) at a target dose during the second phase on Day 1 of the C1, the C2, the C3, the C4, the C5, the C6, and the C7; and wherein lenalidomide is administered to the subject: (i) during the pre-phase on Days 1-21 of the C1; (ii) during the first phase on Days 1-21 of the C1, the C2, the C3, the C4, and the C5; and (iii) during the second phase on Days 1-21 of the C1, the C2, the C3, the C4, the C5, the C6, and the C7.

[0111] In another aspect, provided herein is cevostamab for use in treatment of a subject having an MM with a high-risk cytogenetic feature, the treatment comprising administering to the subject cevostamab and lenalidomide in a dosing regimen comprising: (i) a pre-phase comprising a 28-day dosing cycle (C1); (ii) a first phase, following the pre-phase, comprising a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), and a fifth dosing cycle (C5), wherein each

dosing cycle of the first phase is a 28-day dosing cycle; and (iii) a second phase, following the first phase, comprising a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), a fifth dosing cycle (C5), a sixth dosing cycle (C6), and a seventh dosing cycle (C7), wherein each dosing cycle of the second phase is a 28-day dosing cycle, wherein cevostamab is administered to the subject: (i) at a first step-up dose during the pre-phase on Day 1 of the C1 and as a second step-up dose during the pre-phase on Day 8 of the C1; (ii) at a target dose during the pre-phase on Day 15 of the C1; (iii) at a target dose during the first phase on Days 1 and 15 of the C1, the C2, the C3, the C4, and the C5; and (iv) at a target dose during the second phase on Day 1 of the C1, the C2, the C3, the C4, the C5, the C6, and the C7; and wherein lenalidomide is administered to the subject: (i) during the pre-phase on Days 1-21 of the C1; (ii) during the first phase on Days 1-21 of the C1, the C2, the C3, the C4, and the C5; and (iii) during the second phase on Days 1-21 of the C1, the C2, the C3, the C4, the C5, the C6, and the C7.

[0112] In some aspects: (i) the subject experienced a PR better after induction therapy; (ii) the subject has undergone ASCT within 100 days of the onset of the method and/or has an absence of progressive disease; (iii) the cevostamab and lenalidomide are administered to the patient as a post-transplant maintenance therapy; and (iv) the high-risk cytogenetic feature comprises one or more of the following: translocation events t(4;14) or t(14;16), del(17p), or 1q gain.

[0113] In some aspects: (i) the first step-up dose of cevostamab is 0.3 mg; (ii) the second step-up dose of cevostamab is 3.6 mg; (iii) the target dose of cevostamab is between 90 mg to 198 mg, inclusive; and (iv) lenalidomide is administered at a dose of 10 mg or 15 mg.

[0114] In some aspects, the target dose is 90 mg.

[0115] In some aspects, the target dose is 132 mg.

[0116] In some aspects, the target dose is 160 mg.

BRIEF DESCRIPTION OF THE DRAWING

[0117] FIG. 1 is a schematic diagram of the cevostamab (“cevos”)+lenalidomide (“Len”) substudy for CO43923. D, day.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0118] The term “about” as used herein refers to the usual error range for the respective value readily known to the skilled person in this technical field. Reference to “about” a value or parameter herein includes (and describes) aspects that are directed to that value or parameter per se.

[0119] It is understood that aspects of the invention described herein include “comprising,” “consisting,” and “consisting essentially of” aspects.

[0120] The term “FcRH5” or “fragment crystallizable receptor-like 5,” as used herein, refers to any native FcRH5 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated, and encompasses “full-length,” unprocessed FcRH5, as well as any form of FcRH5 that results from processing in the cell. The term also encompasses naturally occurring variants of FcRH5, including, for example, splice variants or allelic variants. FcRH5 includes,

for example, human FcRH5 protein (UniProtKB/Swiss-Prot ID: Q96RD9.3), which is 977 amino acids in length.

[0121] The terms “anti-FcRH5 antibody” and “an antibody that binds to FcRH5” refer to an antibody that is capable of binding FcRH5 with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting FcRH5. In one embodiment, the extent of binding of an anti-FcRH5 antibody to an unrelated, non-FcRH5 protein is less than about 10% of the binding of the antibody to FcRH5 as measured, e.g., by a radioimmunoassay (RIA). In certain embodiments, an antibody that binds to FcRH5 has a dissociation constant (K_D) of $\leq 1 \mu\text{M}$, $\leq 250 \text{nM}$, $\leq 100 \text{nM}$, $\leq 15 \text{nM}$, $\leq 10 \text{nM}$, $\leq 6 \text{nM}$, $\leq 4 \text{nM}$, $\leq 2 \text{nM}$, $\leq 1 \text{nM}$, $\leq 0.1 \text{nM}$, $\leq 0.01 \text{nM}$, or $\leq 0.001 \text{nM}$ (e.g., 10^{-8} M or less, e.g., from 10^{-8} M to 10^{-13} M). In certain embodiments, an anti-FcRH5 antibody binds to an epitope of FcRH5 that is conserved among FcRH5 from different species.

[0122] The term “cluster of differentiation 3” or “CD3,” as used herein, refers to any native CD3 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated, including, for example, CD3 ϵ , CD3 γ , CD3 α , and CD3 β chains. The term encompasses “full-length,” unprocessed CD3 (e.g., unprocessed or unmodified CD3 ϵ or CD3 γ), as well as any form of CD3 that results from processing in the cell. The term also encompasses naturally occurring variants of CD3, including, for example, splice variants or allelic variants. CD3 includes, for example, human CD3 $\&$ protein (NCBI RefSeq No. NP_000724), which is 207 amino acids in length, and human CD3 γ protein (NCBI RefSeq No. NP_000064), which is 182 amino acids in length.

[0123] The terms “anti-CD3 antibody” and “an antibody that binds to CD3” refer to an antibody that is capable of binding CD3 with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting CD3. In one embodiment, the extent of binding of an anti-CD3 antibody to an unrelated, non-CD3 protein is less than about 10% of the binding of the antibody to CD3 as measured, e.g., by a radioimmunoassay (RIA). In certain embodiments, an antibody that binds to CD3 has a dissociation constant (K_D) of $\leq 1 \mu\text{M}$, $\leq 250 \text{nM}$, $\leq 100 \text{nM}$, $\leq 15 \text{nM}$, $\leq 10 \text{nM}$, $\leq 5 \text{nM}$, $\leq 1 \text{nM}$, $\leq 0.1 \text{nM}$, $\leq 0.01 \text{nM}$, or $\leq 0.001 \text{nM}$ (e.g., 10^{-8} M or less, e.g., from 10^{-8} M to 10^{-13} M , e.g., from 10^{-9} M to 10^{-13} M). In certain embodiments, an anti-CD3 antibody binds to an epitope of CD3 that is conserved among CD3 from different species.

[0124] For the purposes herein, “cevostamab,” also referred to as BFCR4350A or RO7187797, is an Fc-engineered, humanized, full-length non-glycosylated IgG1 kappa T-cell-dependent bispecific antibody (TDB) that binds FcRH5 and CD3 and comprises an anti-FcRH5 arm comprising the heavy chain polypeptide sequence of SEQ ID NO: 35 and the light chain polypeptide sequence of SEQ ID NO: 36 and an anti-CD3 arm comprising the heavy chain polypeptide sequence of SEQ ID NO: 37 and the light chain polypeptide sequence of SEQ ID NO: 38. Cevostamab comprises a threonine to tryptophan amino acid substitution at position 366 on the heavy chain of the anti-FcRH5 arm (T366W) using EU numbering of Fc region amino acid residues and three amino acid substitutions (tyrosine to valine at position 407, threonine to serine at position 366, and leucine to alanine at position 368) on the heavy chain of the anti-CD3 arm (Y407V, T366S, and L368A) using EU

numbering of Fc region amino acid residues to drive heterodimerization of the two arms (half-antibodies). Cevostamab also comprises an amino acid substitution (asparagine to glycine) at position 297 on each heavy chain (N297G) using EU numbering of Fc region amino acid residues, which results in a non-glycosylated antibody that has minimal binding to Fc (Fc γ) receptors and, consequently, prevents Fc-effector function. Cevostamab is also described in WHO Drug Information (International Nonproprietary Names for Pharmaceutical Substances), Recommended INN: List 84, Vol. 34, No. 3, published 2020 (see page 701).

[0125] The term “antibody” herein is used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments (e.g., bis-Fabs) so long as they exhibit the desired antigen-binding activity.

[0126] “Affinity” refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, “binding affinity” refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured by common methods known in the art, including those described herein. Specific illustrative and exemplary aspects for measuring binding affinity are described in the following.

[0127] An “affinity matured” antibody refers to an antibody with one or more alterations in one or more hyper-variable regions (HVRs), compared to a parent antibody which does not possess such alterations, such alterations resulting in an improvement in the affinity of the antibody for antigen.

[0128] The terms “full-length antibody,” “intact antibody,” and “whole antibody” are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure or having heavy chains that contain an Fc region as defined herein.

[0129] An “antibody fragment” refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to bis-Fabs; Fv; Fab; Fab, Fab'-SH; F(ab') $_2$; diabodies; linear antibodies; single-chain antibody molecules (e.g., scFv, ScFab); and multispecific antibodies formed from antibody fragments.

[0130] A “single-domain antibody” refers to an antibody fragment comprising all or a portion of the heavy chain variable domain or all or a portion of the light chain variable domain of an antibody. In certain aspects, a single-domain antibody is a human single-domain antibody (see, e.g., U.S. Pat. No. 6,248,516 B1). Examples of single-domain antibodies include but are not limited to a VH.

[0131] A “Fab” fragment is an antigen-binding fragment generated by papain digestion of antibodies and consists of an entire L chain along with the variable region domain of the H chain (VH), and the first constant domain of one heavy chain (CH1). Papain digestion of antibodies produces two identical Fab fragments. Pepsin treatment of an antibody yields a single large F(ab') $_2$ fragment which roughly corresponds to two disulfide linked Fab fragments having divalent antigen-binding activity and is still capable of cross-

linking antigen. Fab' fragments differ from Fab fragments by having an additional few residues at the carboxy terminus of the CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

[0132] "Fv" consists of a dimer of one heavy- and one light-chain variable region domain in tight, noncovalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although often at a lower affinity than the entire binding site.

[0133] The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain, including native sequence Fc regions and variant Fc regions. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region may be removed, for example, during production or purification of the antibody, or by recombinantly engineering the nucleic acid encoding a heavy chain of the antibody. Accordingly, a composition of intact antibodies may comprise antibody populations with all Lys447 residues removed, antibody populations with no Lys447 residues removed, and antibody populations having a mixture of antibodies with and without the Lys447 residue.

[0134] A "functional Fc region" possesses an "effector function" of a native sequence Fc region. Exemplary "effector functions" include C1q binding; CDC; Fc receptor binding; ADCC; phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor; BCR), etc. Such effector functions generally require the Fc region to be combined with a binding domain (e.g., an antibody variable domain) and can be assessed using various assays as disclosed, for example, in definitions herein.

[0135] A "native sequence Fc region" comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature. Native sequence human Fc regions include a native sequence human IgG1 Fc region (non-A and A allotypes); native sequence human IgG2 Fc region; native sequence human IgG3 Fc region; and native sequence human IgG4 Fc region as well as naturally occurring variants thereof.

[0136] A "variant Fc region" comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification, preferably one or more amino acid substitution(s). Preferably, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or to the Fc region of a parent polypeptide, e.g., from about one to about ten amino acid substitutions, and preferably from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of the parent polypeptide. The variant Fc region herein will preferably

possess at least about 80% homology with a native sequence Fc region and/or with an Fc region of a parent polypeptide, preferably at least about 90% homology therewith, or preferably at least about 95% homology therewith.

[0137] "Fc complex" as used herein refers to CH3 domains of two Fc regions interacting together to form a dimer or, as in certain aspects, two Fc regions interact to form a dimer, wherein the cysteine residues in the hinge regions and/or the CH3 domains interact through bonds and/or forces (e.g., Van der Waals, hydrophobic forces, hydrogen bonds, electrostatic forces, or disulfide bonds).

[0138] "Fc component" as used herein refers to a hinge region, a CH2 domain or a CH3 domain of an Fc region.

[0139] "Hinge region" is generally defined as stretching from about residue 216 to 230 of an IgG (EU numbering), from about residue 226 to 243 of an IgG (Kabat numbering), or from about residue 1 to 15 of an IgG (IMGT unique numbering).

[0140] The "lower hinge region" of an Fc region is normally defined as the stretch of residues immediately C-terminal to the hinge region, i.e., residues 233 to 239 of the Fc region (EU numbering).

[0141] A "variant Fc region" comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification, preferably one or more amino acid substitution(s). Preferably, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or to the Fc region of a parent polypeptide, e.g., from about one to about ten amino acid substitutions, and preferably from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of the parent polypeptide. The variant Fc region herein will preferably possess at least about 80% homology with a native sequence Fc region and/or with an Fc region of a parent polypeptide, and preferably at least about 90% homology therewith, more preferably at least about 95% homology therewith.

[0142] "Fc receptor" or "FcR" describes a receptor that binds to the Fc region of an antibody. A preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one that binds an IgG antibody (a gamma receptor) and includes receptors of the Fc γ RI, Fc γ RII, and Fc γ RIII subclasses, including allelic variants and alternatively spliced forms of these receptors. Fc γ RII receptors include Fc γ RIIA (an "activating receptor") and Fc γ RIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor Fc γ RIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor Fc γ RIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain (see review M. in Daëron, Annu. Rev. Immunol. 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, Annu. Rev. Immunol. 9:457-492 (1991); Capel et al., Immunomethods 4:25-34 (1994); and de Haas et al., J. Lab. Clin. Med. 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., J. Immunol. 117:587 (1976) and Kim et al., J. Immunol. 24:249 (1994)).

[0143] The term "knob-into-hole" or "KnH" technology as mentioned herein refers to the technology directing the pairing of two polypeptides together in vitro or in vivo by

introducing a protuberance (knob) into one polypeptide and a cavity (hole) into the other polypeptide at an interface in which they interact. For example, KnHs have been introduced in the Fc:Fc interaction interfaces, CL:CH1 interfaces or VH/VL interfaces of antibodies (e.g., US2007/0178552, WO 96/027011, WO 98/050431 and Zhu et al. (1997) Protein Science 6:781-788). This is especially useful in driving the pairing of two different heavy chains together during the manufacture of multispecific antibodies. For example, multispecific antibodies having KnH in their Fc regions can further comprise single variable domains linked to each Fc region, or further comprise different heavy chain variable domains that pair with identical, similar, or different light chain variable domains. KnH technology can also be used to pair two different receptor extracellular domains together or any other polypeptide sequences that comprise different target recognition sequences.

[0144] “Framework” or “FR” refers to variable domain residues other than hypervariable region (HVR) residues. The FR of a variable domain generally consists of four FR domains: FR1, FR2, FR3, and FR4. Accordingly, the HVR and FR sequences generally appear in the following sequence in VH (or VL): FR1-H1 (L1)-FR2-H2 (L2)-FR3-H3 (L3)-FR4.

[0145] The “CH1 region” or “CH1 domain” comprises the stretch of residues from about residue 118 to residue 215 of an IgG (EU numbering), from about residue 114 to 223 of an IgG (Kabat numbering), or from about residue 1.4 to residue 121 of an IgG (IMGT unique numbering) (Lefranc et al., IMGT®, the international ImMunoGene Tics information System® 25 years on. Nucleic Acids Res. 2015 January; 43 (Database issue): D413-22).

[0146] The “CH2 domain” of a human IgG Fc region usually extends from about residues 244 to about 360 of an IgG (Kabat numbering), from about residues 231 to about 340 of an IgG (EU numbering), or from about residues 1.6 to about 125 of an IgG (IMGT unique numbering). The CH2 domain is unique in that it is not closely paired with another domain. Rather, two N-linked branched carbohydrate chains are interposed between the two CH2 domains of an intact native IgG molecule. It has been speculated that the carbohydrate may provide a substitute for the domain-domain pairing and help stabilize the CH2 domain. Burton, Molec. Immunol. 22:161-206 (1985).

[0147] The “CH3 domain” comprises the stretch of residues C-terminal to a CH2 domain in an Fc region (i.e., from about amino acid residue 361 to about amino acid residue 478 of an IgG (Kabat numbering), from about amino acid residue 341 to about amino acid residue 447 of an IgG (EU numbering), or from about amino acid residue 1.4 to about amino acid residue 130 of an IgG (IMGT unique numbering)).

[0148] The “CL domain” or “constant light domain” comprises the stretch of residues C-terminal to a light-chain variable domain (VL). The light chain of an antibody may be a kappa (κ) (“C κ ”) or lambda (λ) (“C λ ”) light chain region. The C κ region generally extends from about residue 108 to residue 214 of an IgG (Kabat or EU numbering) or from about residue 1.4 to residue 126 of an IgG (IMGT unique numbering). The CA residue generally extends from about residue 107a to residue 215 (Kabat numbering) or from about residue 1.5 to residue 127 (IMGT unique numbering) (Lefranc et al., IMGT®, the international ImMunoGene Tics

information system® 25 years on. Nucleic Acids Res. 2015 January; 43 (Database issue): D413-22).

[0149] The light chain (LC) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (CH), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated α , δ , γ , ϵ , and μ , respectively. The γ and α classes are further divided into subclasses on the basis of relatively minor differences in CH sequence and function, e.g., humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

[0150] The term “chimeric” antibody refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[0151] The “class” of an antibody refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α , δ , γ , ϵ , and μ , respectively.

[0152] A “human antibody” is one which possesses an amino acid sequence which corresponds to that of an antibody produced by a human or a human cell or derived from a non-human source that utilizes human antibody repertoires or other human antibody-encoding sequences. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues. Human antibodies can be produced using various techniques known in the art, including phage-display libraries. Hoogenboom and Winter. *J. Mol. Biol.* 227:381, 1991; Marks et al. *J. Mol. Biol.* 222:581, 1991. Also available for the preparation of human monoclonal antibodies are methods described in Cole et al. *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985); Boerner et al. *J. Immunol.*, 147 (1): 86-95, 1991. See also van Dijk and van de Winkel. *Curr. Opin. Pharmacol.* 5:368-74, 2001. Human antibodies can be prepared by administering the antigen to a transgenic animal that has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled, e.g., immunized xeno-mice (see, e.g., U.S. Pat. Nos. 6,075,181 and 6,150,584 regarding XENOMOUSE™ technology). See also, for example, Li et al. *Proc. Natl. Acad. Sci. USA.* 103:3557-3562, 2006 regarding human antibodies generated via a human B-cell hybridoma technology.

[0153] A “human consensus framework” is a framework which represents the most commonly occurring amino acid residues in a selection of human immunoglobulin VL or VH framework sequences. Generally, the selection of human immunoglobulin VL or VH sequences is from a subgroup of variable domain sequences. Generally, the subgroup of sequences is a subgroup as in Kabat et al. *Sequences of Proteins of Immunological Interest*, Fifth Edition, NIH Publication 91-3242, Bethesda MD (1991), vols. 1-3. In one aspect, for the VL, the subgroup is subgroup kappa I as in

Kabat et al. *supra*. In one aspect, for the VH, the subgroup is subgroup III as in Kabat et al. *supra*.

[0154] A “humanized” antibody refers to a chimeric antibody comprising amino acid residues from non-human HVRs and amino acid residues from human FRs. In certain aspects, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the HVRs (e.g., CDRs) correspond to those of a non-human antibody, and all or substantially all of the FRs correspond to those of a human antibody. In certain aspects in which all or substantially all of the FRs of a humanized antibody correspond to those of a human antibody, any of the FRs of the humanized antibody may contain one or more amino acid residues (e.g., one or more Vernier position residues of FRs) from non-human FR(s). A humanized antibody optionally may comprise at least a portion of an antibody constant region derived from a human antibody. A “humanized form” of an antibody, e.g., a non-human antibody, refers to an antibody that has undergone humanization.

[0155] The term “variable region” or “variable domain” refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable domains of the heavy chain and light chain (VH and VL, respectively) of a native antibody generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three hypervariable regions (HVRs). (See, e.g., Kindt et al. *Kuby Immunology*, 6th ed. W.H. Freeman and Co., page 91 (2007).) A single VH or VL domain may be sufficient to confer antigen-binding specificity. Furthermore, antibodies that bind a particular antigen may be isolated using a VH or VL domain from an antibody that binds the antigen to screen a library of complementary VL or VH domains, respectively. See, e.g., Portolano et al. *J. Immunol.* 150:880-887, 1993; Clarkson et al. *Nature* 352:624-628, 1991.

[0156] The term “hypervariable region” or “HVR” as used herein refers to each of the regions of an antibody variable domain which are hypervariable in sequence (“complementarity determining regions” or “CDRs”). Generally, antibodies comprise six CDRs: three in the VH (CDR-H1, CDR-H2, CDR-H3), and three in the VL (CDR-L1, CDR-L2, CDR-L3). Exemplary CDRs herein include:

[0157] (a) CDRs occurring at amino acid residues 26-32 (L1), 50-52 (L2), 91-96 (L3), 26-32 (H1), 53-55 (H2), and 96-101 (H3) (Chothia and Lesk, *J. Mol. Biol.* 196:901-917, 1987);

[0158] (b) CDRs occurring at amino acid residues 24-34 (L1), 50-56 (L2), 89-97 (L3), 31-35b (H1), 50-65 (H2), and 95-102 (H3) (Kabat et al. *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991)); and

[0159] (c) antigen contacts occurring at amino acid residues 27c-36 (L1), 46-55 (L2), 89-96 (L3), 30-35b (H1), 47-58 (H2), and 93-101 (H3) (MacCallum et al. *J. Mol. Biol.* 262:732-745, 1996).

[0160] Unless otherwise indicated, HVR residues and other residues in the variable domain (e.g., FR residues) are numbered herein according to Kabat et al. *supra*.

[0161] “Single-chain Fv” also abbreviated as “sFv” or “scFv” are antibody fragments that comprise the VH and VL antibody domains connected into a single polypeptide chain. Preferably, the scFv polypeptide further comprises a poly-

peptide linker between the VH and VL domains, which enables the scFv to form the desired structure for antigen binding. For a review of scFv, see Pluckthun, *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); Malmborg et al., *J. Immunol. Methods* 183:7-13, 1995.

[0162] By “targeting domain” is meant a part of a compound or a molecule that specifically binds to a target epitope, antigen, ligand, or receptor. Targeting domains include but are not limited to antibodies (e.g., monoclonal, polyclonal, recombinant, humanized, and chimeric antibodies), antibody fragments or portions thereof (e.g., bis-Fab fragments, Fab fragments, F(ab')₂, scFab, scFv antibodies, SMIP, single-domain antibodies, diabodies, minibodies, scFv-Fc, affibodies, nanobodies, and VH and/or VL domains of antibodies), receptors, ligands, aptamers, peptide targeting domains (e.g., cysteine knot proteins (CKP)), and other molecules having an identified binding partner. A targeting domain may target, block, agonize, or antagonize the antigen to which it binds.

[0163] The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variant antibodies, e.g., containing naturally occurring mutations or arising during production of a monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. Thus, the modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by a variety of techniques, including but not limited to the hybridoma method, recombinant DNA methods, phage-display methods, and methods utilizing transgenic animals containing all or part of the human immunoglobulin loci, such methods and other exemplary methods for making monoclonal antibodies being described herein.

[0164] The term “multispecific antibody” is used in the broadest sense and specifically covers an antibody that has polyepitopic specificity. In one aspect, the multispecific antibody binds to two different targets (e.g., bispecific antibody). Such multispecific antibodies include, but are not limited to, an antibody comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), where the VH/VL unit has polyepitopic specificity, antibodies having two or more VL and VH domains with each VH/VL unit binding to a different epitope, antibodies having two or more single variable domains with each single variable domain binding to a different epitope, full-length antibodies, antibody fragments such as Fab, Fv, dsFv, scFv, diabodies, bispecific diabodies and triabodies, antibody fragments that have been linked covalently or non-covalently. “Polyepitopic specificity” refers to the ability to specifically bind to two or more different epitopes on the same or different target(s). “Monospecific” refers to the ability to bind only

one antigen. In one aspect, the monospecific biepitopic antibody binds two different epitopes on the same target/antigen. In one aspect, the monospecific polyepitopic antibody binds to multiple different epitopes of the same target/antigen. According to one aspect, the multispecific antibody is an IgG antibody that binds to each epitope with an affinity of 5 μ M to 0.001 pM, 3 μ M to 0.001 pM, 1 μ M to 0.001 pM, 0.5 μ M to 0.001 pM, or 0.1 μ M to 0.001 pM.

[0165] A “naked antibody” refers to an antibody that is not conjugated to a heterologous moiety (e.g., a cytotoxic moiety) or radiolabel. The naked antibody may be present in a pharmaceutical formulation.

[0166] “Native antibodies” refer to naturally occurring immunoglobulin molecules with varying structures. For example, native IgG antibodies are heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light chains and two identical heavy chains that are disulfide-bonded. From N- to C-terminus, each heavy chain has a variable region (VH), also called a variable heavy domain or a heavy chain variable domain, followed by three constant domains (CH1, CH2, and CH3). Similarly, from N- to C-terminus, each light chain has a variable region (VL), also called a variable light domain or a light chain variable domain, followed by a constant light (CL) domain. The light chain of an antibody may be assigned to one of two types, called kappa (κ) and lambda (λ), based on the amino acid sequence of its constant domain.

[0167] As used herein, the term “immunoadhesin” designates molecules which combine the binding specificity of a heterologous protein (an “adhesin”) with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with a desired binding specificity, which amino acid sequence is other than the antigen recognition and binding site of an antibody (i.e., is “heterologous” compared to a constant region of an antibody), and an immunoglobulin constant domain sequence (e.g., CH2 and/or CH3 sequence of an IgG). The adhesin and immunoglobulin constant domains may optionally be separated by an amino acid spacer. Exemplary adhesin sequences include contiguous amino acid sequences that comprise a portion of a receptor or a ligand that binds to a protein of interest. Adhesin sequences can also be sequences that bind a protein of interest, but are not receptor or ligand sequences (e.g., adhesin sequences in peptibodies). Such polypeptide sequences can be selected or identified by various methods, include phage display techniques and high throughput sorting methods. The immunoglobulin constant domain sequence in the immunoadhesin can be obtained from any immunoglobulin, such as IgG1, IgG2, IgG3, or IgG4 subtypes, IgA (including IgA1 and IgA2), IgE, IgD, or IgM.

[0168] “Chemotherapeutic agent” includes chemical compounds useful in the treatment of cancer. Examples of chemotherapeutic agents include erlotinib (TARCEVA®, Genentech/OSI Pharm.), bortezomib (VELCADE®, Millennium Pharm.), disulfiram, epigallocatechin gallate, salinosporamide A, carfilzomib, 17-AAG (geldanamycin), radicicol, lactate dehydrogenase A (LDH-A), fulvestrant (FASLODEX®, AstraZeneca), sunitinib (SUTENT®, Pfizer/Sugen), letrozole (FEMARA®, Novartis), imatinib mesylate (GLEEVEC®, Novartis), finasunate (VATALANIB®, Novartis), oxaliplatin (ELOXATIN®, Sanofi), 5-FU (5-fluorouracil), leucovorin, Rapamycin (Sirolimus, RAPAMUNE®, Wyeth), Lapatinib (TYKERB®, GSK572016,

Glaxo Smith Kline), Lonafoxib (SCH 66336), sorafenib (NEXAVAR®, Bayer Labs), gefitinib (IRESSA®, AstraZeneca), AG1478, alkylating agents such as thiotepa and CYTOXAN® cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylolmelamine; acetogenins (especially bullatacin and bullatacinone);

[0169] a camptothecin (including topotecan and irinotecan); bryostatin; calystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); adrenocorticosteroids (including prednisone and prednisolone); cyproterone acetate; 5x-reductases including finasteride and dutasteride); vorinostat, romidepsin, panobinostat, valproic acid, mocetinostat dolastatin; aldesleukin, talc duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chloramphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin γ 1I and calicheamicin ω 1I (Angew Chem. Int. Ed. Engl. 1994 33:183-186); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin), morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodoxorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteroferone, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thioguanine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as folinic acid; aceglactone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestramycin; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; moidamnol; niraerine; pentostatin; phenacet; pirarubicin; losoxantrone; podophyllin acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2'-

trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; piperbroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thioptera; taxoids, e.g., TAXOL (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAZAXANE® (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, Ill.), and TAXOTERE® (docetaxel, doxetaxel; Sanofi-Aventis); chlorambucil; GEMZAR® (gemcitabine); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® (vinorelbine); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0170] Chemotherapeutic agent also includes (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, iodoxyfene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifene citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4 (5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestan, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide and goserelin; buserelin, triptorelin, medroxyprogesterone acetate, diethylstibestrol, premarin, fluoxymesterone, all transretionic acid, fenretinide, as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors; (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-alpha, Ralf and H-Ras; (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN®, rIL-2; a topoisomerase 1 inhibitor such as LURTOTECAN®; ABARELIX® rmRH; and (ix) pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0171] Chemotherapeutic agent also includes antibodies such as alemtuzumab (Campath), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), pertuzumab (OMNITARG®, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), tositumomab (Bexxar, Corixia), and the antibody drug conjugate, gemtuzumab ozogamicin (MYLOTARG®, Wyeth). Additional humanized monoclonal antibodies with therapeutic potential as agents in combination with the compounds of the invention include: apolizumab, aselizumab, atlizumab, bapinezumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cildusituzumab, ciltuzumab, daclizumab,

eculizumab, efalizumab, epratuzumab, erlizumab, felizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, linatumab, matuzumab, mepolizumab, motavizumab, motivizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pectusituzumab, pectuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, siplizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, urtoxazumab, ustekinumab, visilizumab, and the anti-interleukin-12 (ABT-874/J695, Wyeth Research and Abbott Laboratories) which is a recombinant exclusively human-sequence, full-length IgG1λ antibody genetically modified to recognize interleukin-12 p40 protein.

[0172] Chemotherapeutic agent also includes "EGFR inhibitors," which refers to compounds that bind to or otherwise interact directly with EGFR and prevent or reduce its signaling activity, and is alternatively referred to as an "EGFR antagonist." Examples of such agents include antibodies and small molecules that bind to EGFR. Examples of antibodies which bind to EGFR include MAb 579 (ATCC CRL HB 8506), MAb 455 (ATCC CRL HB8507), MAb 225 (ATCC CRL 8508), MAb 528 (ATCC CRL 8509) (see, U.S. Pat. No. 4,943,533, Mendelsohn et al.) and variants thereof, such as chimerized 225 (C225 or Cetuximab; ERBITUX®) and reshaped human 225 (H225) (see, WO 96/40210, Imclone Systems Inc.); IMC-11F8, a fully human, EGFR-targeted antibody (Imclone); antibodies that bind type II mutant EGFR (U.S. Pat. No. 5,212,290); humanized and chimeric antibodies that bind EGFR as described in U.S. Pat. No. 5,891,996; and human antibodies that bind EGFR, such as ABX-EGF or Panitumumab (see WO98/50433, Abgenix/Amgen); EMD 55900 (Stragliotto et al. Eur. J. Cancer 32A: 636-640 (1996)); EMD7200 (matuzumab) a humanized EGFR antibody directed against EGFR that competes with both EGF and TGF-alpha for EGFR binding (EMD/Merck); human EGFR antibody, HuMax-EGFR (GenMab); fully human antibodies known as E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 and E7.6. 3 and described in U.S. Pat. No. 6,235,883; MDX-447 (Medarex Inc); and mAb 806 or humanized mAb 806 (Johns et al., J. Biol. Chem. 279 (29): 30375-30384 (2004)). The anti-EGFR antibody may be conjugated with a cytotoxic agent, thus generating an immunoconjugate (see, e.g., EP659,439A2, Merck Patent GmbH). EGFR antagonists include small molecules such as compounds described in U.S. Pat. Nos. 5,616,582, 5,457,105, 5,475,001, 5,654,307, 5,679,683, 6,084,095, 6,265,410, 6,455,534, 6,521,620, 6,596,726, 6,713,484, 5,770,599, 6,140,332, 5,866,572, 6,399,602, 6,344,459, 6,602,863, 6,391,874, 6,344,455, 5,760,041, 6,002,008, and 5,747,498, as well as the following PCT publications: WO98/14451, WO98/50038, WO99/09016, and WO99/24037. Particular small molecule EGFR antagonists include OSI-774 (CP-358774, erlotinib, TARCEVA® Genentech/OSI Pharmaceuticals); PD 183805 (CI 1033, 2-propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride, Pfizer Inc.); ZD1839, gefitinib (IRESSA®) 4-(3'-Chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy) quinazoline, AstraZeneca); ZM 105180 ((6-amino-4-(3-methylphenylamino)-quinazoline, Zeneca); BIBX-1382 (N8-(3-chloro-4-

fluoro-phenyl)-N2-(1-methyl-piperidin-4-yl)-pyrimido[5,4-d]pyrimidine-2,8-diamine, Boehringer Ingelheim); PKI-166 ((R)-4-[4-[(1-phenylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-6-yl]-phenol); (R)-6-(4-hydroxyphenyl)-4-[(1-phenylethyl)amino]-7H-pyrrolo[2,3-d]pyrimidine); CL-387785 (N-[4-[(3-bromophenyl)amino]-6-quinazolinyl]-2-butynamide); EKB-569 (N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-ethoxy-6-quinoliny]-4-(dimethylamino)-2-butenamide) (Wyeth); AG1478 (Pfizer); AG1571 (SU 5271; Pfizer); dual EGFR/HER2 tyrosine kinase inhibitors such as lapatinib (TYKERB®, GSK572016 or N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5[[2methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine).

[0173] Chemotherapeutic agents also include “tyrosine kinase inhibitors” including the EGFR-targeted drugs noted in the preceding paragraph; small molecule HER2 tyrosine kinase inhibitor such as TAK165 available from Takeda; CP-724,714, an oral selective inhibitor of the ErbB2 receptor tyrosine kinase (Pfizer and OSI); dual-HER inhibitors such as EKB-569 (available from Wyeth) which preferentially binds EGFR but inhibits both HER2 and EGFR-overexpressing cells; lapatinib (GSK572016; available from Glaxo-SmithKline), an oral HER2 and EGFR tyrosine kinase inhibitor; PKI-166 (available from Novartis); pan-HER inhibitors such as canertinib (CI-1033; Pharmacia); Raf-1 inhibitors such as antisense agent ISIS-5132 available from ISIS Pharmaceuticals which inhibit Raf-1 signaling; non-HER targeted TK inhibitors such as imatinib mesylate (GLEEVEC®, available from Glaxo SmithKline); multi-targeted tyrosine kinase inhibitors such as sunitinib (SUTENT®, available from Pfizer); VEGF receptor tyrosine kinase inhibitors such as vatalanib (PTK787/ZK222584, available from Novartis/Schering AG); MAPK extracellular regulated kinase I inhibitor CI-1040 (available from Pharmacia); quinazolines, such as PD 153035,4-(3-chloroanilino) quinazoline; pyridopyrimidines; pyrimidopyrimidines; pyrrolopyrimidines, such as CGP 59326, CGP 60261 and CGP 62706; pyrazolopyrimidines, 4-(phenylamino)-7H-pyrrolo[2,3-d]pyrimidines; curcumin (diferuloyl methane, 4,5-bis(4-fluoroanilino)phthalimide); tryphostins containing nitrothiophene moieties; PD-0183805 (Warner-Lamber); antisense molecules (e.g. those that bind to HER-encoding nucleic acid); quinoxalines (U.S. Pat. No. 5,804,396); tryphostins (U.S. Pat. No. 5,804,396); ZD6474 (AstraZeneca); PTK-787 (Novartis/Schering AG); pan-HER inhibitors such as CI-1033 (Pfizer); Affinitac (ISIS 3521; Isis/Lilly); imatinib mesylate (GLEEVEC®); PKI 166 (Novartis); GW2016 (Glaxo SmithKline); CI-1033 (Pfizer); EKB-569 (Wyeth); Semaxinib (Pfizer); ZD6474 (AstraZeneca); PTK-787 (Novartis/Schering AG); INC-1C11 (Imclone), rapamycin (sirolimus, RAPAMUNE®); or as described in any of the following patent publications: U.S. Pat. No. 5,804,396; WO 1999/09016 (American Cyanamid); WO 1998/43960 (American Cyanamid); WO 1997/38983 (Warner Lambert); WO 1999/06378 (Warner Lambert); WO 1999/06396 (Warner Lambert); WO 1996/30347 (Pfizer, Inc); WO 1996/33978 (Zeneca); WO 1996/3397 (Zeneca) and WO 1996/33980 (Zeneca).

[0174] Chemotherapeutic agents also include dexamethasone, interferons, colchicine, metoprine, cyclosporine, amphotericin, metronidazole, alemtuzumab, alitretinoin, allopurinol, amifostine, arsenic trioxide, asparaginase, BCG live, bevacizumab, bexarotene, cladribine, clofarabine, darbepoetin alfa, denileukin, dextrazoxane, epoetin alfa, elo-

tinib, filgrastim, histrelin acetate, ibritumomab, interferon alfa-2a, interferon alfa-2b, lenalidomide, levamisole, mesna, methoxsalen, nandrolone, nelarabine, nefetumomab, oprelvekin, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, plicamycin, porfimer sodium, quinacrine, rasburicase, sargramostim, temozolamide, VM-26, 6-TG, toremifene, tretinoin, ATRA, valrubicin, zoledronate, and zoledronic acid, and pharmaceutically acceptable salts thereof.

[0175] Chemotherapeutic agents also include hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, triamcinolone acetonide, triamcinolone alcohol, mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, flucortolone, hydrocortisone-17-butyrate, hydrocortisone-17-valerate, aclometasone dipropionate, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate, flucortolone caproate, flucortolone pivalate and fluprednidene acetate; immune selective anti-inflammatory peptides (ImSAIDs) such as phenylalanine-glutamine-glycine (FEG) and its D-isomeric form (fcG) (IMULAN Bio-Therapeutics, LLC); anti-rheumatic drugs such as azathioprine, cyclosporin (cyclosporine A), D-penicillamine, gold salts, hydroxychloroquine, lefunomide/minocycline, sulfasalazine, tumor necrosis factor alpha (TNF α) blockers such as etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi), interleukin 1 (IL-1) blockers such as anakinra (Kineret), T cell costimulation blockers such as abatacept (Orencia), interleukin 6 (IL-6) blockers such as tocilizumab (ACTEMRA®); interleukin 13 (IL-13) blockers such as lebrikizumab; interferon alpha (IFN) blockers such as rontalizumab; beta 7 integrin blockers such as rhuMAb Beta7; IgE pathway blockers such as Anti-M1 prime; secreted homotrimeric LT α 3 and membrane bound heterotrimer LT α 1/B2 blockers such as anti-lymphotoxin alpha (LT α); radioactive isotopes (e.g., At 211 , I 131 , I 125 , Y 90 , Re 186 , Re 188 , Sm 153 , Bi 212 , P 32 , Pb 212 , and radioactive isotopes of Lu); miscellaneous investigational agents such as thioplatin, PS-341, phenylbutyrate, ET-18-OCH $_3$, or farnesyl transferase inhibitors (L-739749, L-744832); polyphenols such as quercetin, resveratrol, piceatannol, epigallocatechine gallate, theaflavins, flavanols, procyanidins, betulinic acid and derivatives thereof; autophagy inhibitors such as chloroquine; delta-9-tetrahydrocannabinol (dronabinol, MARI-NOL®); beta-lapachone; lapachol; colchicines; betulinic acid; acetylcampothecin, scopolectin, and 9-aminocampothecin); podophyllotoxin; tegafur (UFTORAL®); bexarotene (TARGRETIN®); bisphosphonates such as clodronate (for example, BONEFOS® or OSTAC®), etidronate (DIDROCAL®), NE-58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); and epidermal growth factor receptor (EGF-R); vaccines such as THERATOPE® vaccine; perifosine, COX-2 inhibitor (e.g., celecoxib or etoricoxib), proteosome inhibitor (e.g., PS341); CCI-779; tipifarnib (R11577); orafenib, ABT-510; Bcl-2 inhibitor such as oblimersen sodium (GENASENSE®); pixantrone; farnesyltransferase inhibitors such as lonafarnib (SCH 6636, SARASARTM); and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more

of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone; and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin (ELOXATIN™) combined with 5-FU and leucovorin.

[0176] Chemotherapeutic agents also include non-steroidal anti-inflammatory drugs with analgesic, antipyretic and anti-inflammatory effects. NSAIDs include non-selective inhibitors of the enzyme cyclooxygenase. Specific examples of NSAIDs include aspirin, propionic acid derivatives such as ibuprofen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin and naproxen, acetic acid derivatives such as indometacin, sulindac, etodolac, diclofenac, enolic acid derivatives such as piroxicam, meloxicam, tenoxicam, dixamic, lornoxicam and isoxicam, fenamic acid derivatives such as mefenamic acid, meclofenamic acid, flufenamic acid, tolafenamic acid, and COX-2 inhibitors such as celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, and valdecoxib. NSAIDs can be indicated for the symptomatic relief of conditions such as rheumatoid arthritis, osteoarthritis, inflammatory arthropathies, ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, acute gout, dysmenorrhoea, metastatic bone pain, headache and migraine, postoperative pain, mild-to-moderate pain due to inflammation and tissue injury, pyrexia, ileus, and renal colic.

[0177] The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents a cellular function and/or causes cell death or destruction. Cytotoxic agents include, but are not limited to, radioactive isotopes (e.g., At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², Pb²¹², and radioactive isotopes of Lu); chemotherapeutic agents or drugs (e.g., methotrexate, vinca alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents); growth inhibitory agents; enzymes and fragments thereof such as nucleolytic enzymes; antibiotics; toxins such as

conditions which predispose a mammal to the disorder in question. In one aspect, the disorder is a cancer, e.g., a multiple myeloma (MM).

[0179] The terms "cell proliferative disorder" and "proliferative disorder" refer to disorders that are associated with some degree of abnormal cell proliferation. In one aspect, the cell proliferative disorder is cancer. In one aspect, the cell proliferative disorder is a tumor.

[0180] "Tumor," as used herein, refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues. The terms "cancer," "cancerous," "cell proliferative disorder," "proliferative disorder," and "tumor" are not mutually exclusive as referred to herein.

[0181] The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth/proliferation. Aspects of cancer include solid tumor cancers and non-solid tumor cancers. Examples of cancer include, but are not limited to, B cell proliferative disorders, such as multiple myeloma (MM), which may be relapsed or refractory MM. The MM may be, e.g., typical MM (e.g., immunoglobulin G (IgG) MM, IgA MM, IgD MM, IgE MM, or IgM MM), light chain MM (LCMM) (e.g., lambda light chain MM or kappa light chain MM), or non-secretory MM. The MM may be newly diagnosed MM (NDMM).

[0182] The MM may have one or more cytogenetic features. In some examples, the cytogenetic feature is a "high-risk cytogenetic feature," e.g., t(4;14), t(11;14), t(14;16), and/or del(17p), as described in Table 1 and in the International Myeloma Working Group (IMWG) criteria provided in Sonneveld et al., *Blood*, 127 (24): 2955-2962, 2016, which is incorporated herein by reference in its entirety, and/or 1q21, as described in Chang et al., *Bone Marrow Transplantation*, 45:117-121, 2010, which is incorporated herein by reference in its entirety. In some examples, the high-risk cytogenetic feature includes one or more of the following (i) translocation events: t(4;14), t(14;16) (IMWG criteria); deletion (del) (17p) (IMWG criteria); or gain in chromosome 1q. Cytogenetic features may be detected, e.g., using fluorescent in situ hybridization (FISH).

TABLE 1

Cytogenetic features of MM			
Primary genetic events		Secondary genetic events	
IgH translocation	Gene(s)	Deletion	Gene(s)
t(4; 14)	FGFR3/MMSET	1p	CDKN2C, FAF1, FAM46C
t(6; 14)	CCND3	6q	
t(11; 14)	CCND1	8p	
t(14; 16)	MAF	13	RB1, DIS3
t(14; 20)	MAFB	11g 14g 16q 17p	BIRC2/BIRC3 TRAF3 WWOX, CYLD TP53
Hyperdiploidy		Gain	
Trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, 21		1q	CKS1B, ANP32E

small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof; and the various antitumor or anti-cancer agents disclosed below.

[0178] A "disorder" is any condition that would benefit from treatment including, but not limited to, chronic and acute disorders or diseases including those pathological

[0183] The term "B cell proliferative disorder" or "B cell malignancy" refers to a disorder that is associated with some degree of abnormal B cell proliferation and includes, for example, a lymphoma, leukemia, myeloma, and myelodysplastic syndrome. In one embodiment, the B cell proliferative disorder is a lymphoma, such as non-Hodgkin's lymphoma (NHL), including, for example, diffuse large B cell

lymphoma (DLBCL) (e.g., relapsed or refractory DLBCL). In another embodiment, the B cell proliferative disorder is a leukemia, such as chronic lymphocytic leukemia (CLL). Other specific examples of cancer also include germinal-center B cell-like (GCB) diffuse large B cell lymphoma (DLBCL), activated B cell-like (ABC) DLBCL, follicular lymphoma (FL), mantle cell lymphoma (MCL), acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL), marginal zone lymphoma (MZL), small lymphocytic leukemia (SLL), lymphoplasmacytic lymphoma (LL), Waldenstrom macroglobulinemia (WM), central nervous system lymphoma (CNSL), Burkitt's lymphoma (BL), B cell prolymphocytic leukemia, splenic marginal zone lymphoma, hairy cell leukemia, splenic lymphoma/leukemia, unclassifiable, splenic diffuse red pulp small B cell lymphoma, hairy cell leukemia variant, heavy chain diseases, α heavy chain disease, γ heavy chain disease, μ heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone, extraosseous plasmacytoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), nodal marginal zone lymphoma, pediatric nodal marginal zone lymphoma, primary follicular lymphoma, primary cutaneous follicle center lymphoma, T cell/histiocyte rich large B cell lymphoma, primary DLBCL of the CNS, primary cutaneous DLBCL, leg type, EBV-positive DLBCL of the elderly, DLBCL associated with chronic inflammation, lymphomatoid granulomatosis, primary mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, ALK-positive large B cell lymphoma, plasmablastic lymphoma, large B cell lymphoma arising in HHV8-associated multicentric Castleman disease, primary effusion lymphoma: B cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma, and B cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin's lymphoma. Further examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies, including B cell lymphomas. More particular examples of such cancers include, but are not limited to, low grade/follicular NHL; small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; AIDS-related lymphoma; and acute lymphoblastic leukemia (ALL); chronic myeloblastic leukemia; and post-transplant lymphoproliferative disorder (PTLD). Examples of solid tumors include squamous cell cancer (e.g., epithelial squamous cell cancer), lung cancer including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer and gastrointestinal stromal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, cancer of the urinary tract, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, melanoma, superficial spreading melanoma, lentigo maligna melanoma, acral lentiginous melanomas, nodular melanomas, as well as abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors),

Meigs' syndrome, brain, as well as head and neck cancer, and associated metastases. In certain embodiments, cancers that are amenable to treatment by the antibodies disclosed herein include breast cancer, colorectal cancer, rectal cancer, non-small cell lung cancer, glioblastoma, non-Hodgkins lymphoma (NHL), renal cell cancer, prostate cancer, liver cancer, pancreatic cancer, soft-tissue sarcoma, Kaposi's sarcoma, carcinoid carcinoma, head and neck cancer, ovarian cancer, and mesothelioma.

[0184] The term "FcRH5-positive cancer" refers to a cancer comprising cells that express FcRH5 on their surface. For the purposes of determining whether a cell expresses FcRH5 on the surface, FcRH5 mRNA expression is considered to correlate to FcRH5 expression on the cell surface. In some embodiments, expression of FcRH5 mRNA is determined by a method selected from in situ hybridization and RT-PCR (including quantitative RT-PCR). Alternatively, expression of FcRH5 on the cell surface can be determined, for example, using antibodies to FcRH5 in a method such as immunohistochemistry, FACS, etc. In some embodiments, FcRH5 is one or more of FcRH5a, FcRH5b, FcRH5c, UniProt Identifier Q96RD9-2, and/or FcRH5d. In some embodiments, the FcRH5 is FcRH5c. For example, the FcRH5-positive cancer may be FcRH5-positive MM.

[0185] "Effector functions" refer to those biological activities attributable to the Fc region of an antibody, which vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor); and B cell activation.

[0186] "Complement dependent cytotoxicity" or "CDC" refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) that are bound to their cognate antigen. To assess complement activation, a CDC assay, e.g., as described in Gazzano-Santoro et al., *J. Immunol. Methods* 202:163 (1996), can be performed.

[0187] "Antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to a form of cytotoxicity in which secreted Ig bound onto Fc receptors (FcRs) present on certain cytotoxic cells (e.g., Natural Killer (NK) cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxic agents. The antibodies "arm" the cytotoxic cells and are absolutely required for such killing. The primary cells for mediating ADCC, NK cells, express Fc γ RIII only, whereas monocytes express Fc γ RI, Fc γ RII, and Fc γ RIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet. *Annu. Rev. Immunol.* 9:457-92, 1991. To assess ADCC activity of a molecule of interest, an in vitro ADCC assay, such as that described in U.S. Pat. No. 5,500,362 or 5,821,337 can be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest can be assessed in vivo, e.g., in an animal model such as that disclosed in Clynes et al. *Proc. Natl. Acad. Sci. USA.* 95:652-656, 1998.

[0188] “Complex” or “complexed” as used herein refers to the association of two or more molecules that interact with each other through bonds and/or forces (e.g., Van der Waals, hydrophobic, hydrophilic forces) that are not peptide bonds. In one aspect, the complex is heteromultimeric. It should be understood that the term “protein complex” or “polypeptide complex” as used herein includes complexes that have a non-protein entity conjugated to a protein in the protein complex (e.g., including, but not limited to, chemical molecules such as a toxin or a detection agent).

[0189] As used herein, “delaying progression” of a disorder or disease means to defer, hinder, slow, retard, stabilize, and/or postpone development of the disease or disorder (e.g., a cell proliferative disorder, e.g., cancer). This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease. For example, a late-stage cancer, such as development of metastasis, may be delayed.

[0190] An “effective amount” of a compound, for example, an anti-FcRH5/anti-CD3 T-cell-dependent bispecific antibody (TDB) disclosed herein, lenalidomide, or a composition (e.g., pharmaceutical composition) thereof (e.g., a pharmaceutical composition that includes an anti-FcRH5/anti-CD3 TDB as disclosed herein and/or lenalidomide), is at least the minimum amount required to achieve the desired therapeutic or prophylactic result, such as a measurable improvement or prevention of a particular disorder (e.g., a cell proliferative disorder, e.g., cancer, e.g., MM, e.g., MM with a high-risk cytogenetic feature). An effective amount herein may vary according to factors such as the disease state, age, sex, and weight of the patient, and the ability of the antibody to elicit a desired response in the individual. An effective amount is also one in which any toxic or detrimental effects of the treatment are outweighed by the therapeutically beneficial effects. For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity, or delaying the onset of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications, and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such as via targeting, delaying the progression of the disease, and/or prolonging survival. In the case of cancer or tumor, an effective amount of the drug may have the effect in reducing the number of cancer cells; reducing the tumor size; inhibiting (i.e., slow to some extent or desirably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and desirably stop) tumor metastasis; inhibiting to some extent tumor growth; and/or relieving to some extent one or more of the symptoms associated with the disorder. An effective amount can be administered in one or more administrations. For purposes of this invention, an effective amount of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective amount of a drug, compound, or pharmaceutical composition may or

may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an “effective amount” may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

[0191] As used herein, “overall survival” or “OS” refers to the percentage of individuals in a group who are likely to be alive after a particular duration of time.

[0192] As used herein, “objective response rate” (ORR) refers to the sum of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) rates as determined using the International Myeloma Working Group response criteria (Table 8).

[0193] The term “epitope” refers to the particular site on an antigen molecule to which an antibody binds. In some aspects, the particular site on an antigen molecule to which an antibody binds is determined by hydroxyl radical footprinting. In some aspects, the particular site on an antigen molecule to which an antibody binds is determined by crystallography.

[0194] A “growth inhibitory agent” when used herein refers to a compound or composition which inhibits growth of a cell either *in vitro* or *in vivo*. In one aspect, growth inhibitory agent is growth inhibitory antibody that prevents or reduces proliferation of a cell expressing an antigen to which the antibody binds. In another aspect, the growth inhibitory agent may be one which significantly reduces the percentage of cells in S phase. Aspects of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxanes, and topoisomerase II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in Mendelsohn and Israel, eds., *The Molecular Basis of Cancer*, Chapter 1, entitled “Cell cycle regulation, oncogenes, and antineoplastic drugs” by Murakami et al. (W.B. Saunders, Philadelphia, 1995), e.g., p. 13. The taxanes (paclitaxel and docetaxel) are anticancer drugs both derived from the yew tree. Docetaxel (TAXOTERE®, Rhone-Poulenc Rorer), derived from the European yew, is a semisynthetic analogue of paclitaxel (TAXOL®, Bristol-Myers Squibb). Paclitaxel and docetaxel promote the assembly of microtubules from tubulin dimers and stabilize microtubules by preventing depolymerization, which results in the inhibition of mitosis in cells.

[0195] An “immunoconjugate” is an antibody conjugated to one or more heterologous molecule(s), including but not limited to a cytotoxic agent.

[0196] The term “immunomodulatory agent” or “IMID” refers to a class of molecules that modifies the immune system response or the functioning of the immune system. Immunomodulatory agents include, but are not limited to, PD-1 axis binding antagonists, thalidomide (α -N-phthalimido-glutarimide) and its analogues, OTEZLA® (apremi-

last), REVLIMID® (lenalidomide) and POMALYST® (pomalidomide), and pharmaceutically acceptable salts or acids thereof.

[0197] A “subject” or an “individual” is a mammal. Mammals include, but are not limited to, domesticated animals (e.g., cows, sheep, cats, dogs, and horses), primates (e.g., humans and non-human primates such as monkeys), rabbits, and rodents (e.g., mice and rats). In certain aspects, the subject or individual is a human. In certain aspects, the subject or individual is a patient, e.g., a human patient.

[0198] An “isolated” protein or peptide is one which has been separated from a component of its natural environment. In some aspects, a protein or peptide is purified to greater than 95% or 99% purity as determined by, for example, electrophoresis (e.g., SDS-PAGE, isoelectric focusing (IEF), capillary electrophoresis) or chromatography (e.g., ion exchange or reverse phase HPLC).

[0199] An “isolated” nucleic acid refers to a nucleic acid molecule that has been separated from a component of its natural environment. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally or at a chromosomal location that is different from its natural chromosomal location.

[0200] The term “PD-1 axis binding antagonist” refers to a molecule that inhibits the interaction of a PD-1 axis binding partner with either one or more of its binding partners, so as to remove T-cell dysfunction resulting from signaling on the PD-1 signaling axis, with a result being to restore or enhance T-cell function (e.g., proliferation, cytokine production, and/or target cell killing). As used herein, a PD-1 axis binding antagonist includes a PD-L1 binding antagonist, a PD-1 binding antagonist, and a PD-L2 binding antagonist. In some instances, the PD-1 axis binding antagonist includes a PD-L1 binding antagonist or a PD-1 binding antagonist. In a preferred aspect, the PD-1 axis binding antagonist is a PD-L1 binding antagonist.

[0201] The term “PD-L1 binding antagonist” refers to a molecule that decreases, blocks, inhibits, abrogates, or interferes with signal transduction resulting from the interaction of PD-L1 with either one or more of its binding partners, such as PD-1 and/or B7-1. In some instances, a PD-L1 binding antagonist is a molecule that inhibits the binding of PD-L1 to its binding partners. In a specific aspect, the PD-L1 binding antagonist inhibits binding of PD-L1 to PD-1 and/or B7-1. In some instances, the PD-L1 binding antagonists include anti-PD-L1 antibodies, antigen-binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of PD-L1 with one or more of its binding partners, such as PD-1 and/or B7-1. In one instance, a PD-L1 binding antagonist reduces the negative co-stimulatory signal mediated by or through cell surface proteins expressed on T lymphocytes mediated signaling through PD-L1 so as to render a dysfunctional T-cell less dysfunctional (e.g., enhancing effector responses to antigen recognition). In some instances, the PD-L1 binding antagonist binds to PD-L1. In some instances, a PD-L1 binding antagonist is an anti-PD-L1 antibody (e.g., an anti-PD-L1 antagonist antibody). Exemplary anti-PD-L1 antagonist antibodies include atezolizumab, MDX-1105, MEDI4736 (durvalumab), MSB0010718C (avelumab), SHR-1316, CS1001, envafoli-

mab, TQB2450, ZKAB001, LP-002, CX-072, IMC-001, KL-A167, APL-502, cosibelimab, lodapolimab, FAZ053, TG-1501, BGB-A333, BCD-135, AK-106, LDP, GR1405, HLX20, MSB2311, RC98, PDL-GEX, KD036, KY1003, YBL-007, and HS-636. In some aspects, the anti-PD-L1 antibody is atezolizumab, MDX-1105, MEDI4736 (durvalumab), or MSB0010718C (avelumab). In one specific aspect, the PD-L1 binding antagonist is MDX-1105. In another specific aspect, the PD-L1 binding antagonist is MEDI4736 (durvalumab). In another specific aspect, the PD-L1 binding antagonist is MSB0010718C (avelumab). In other aspects, the PD-L1 binding antagonist may be a small molecule, e.g., GS-4224, INCB086550, MAX-10181, INCB090244, CA-170, or ABSK041, which in some instances may be administered orally. Other exemplary PD-L1 binding antagonists include AVA-004, MT-6035, VXM10, LYN192, GB7003, and JS-003. In a particular aspect, the PD-L1 binding antagonist is atezolizumab.

[0202] The term “PD-1 binding antagonist” refers to a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-1 with one or more of its binding partners, such as PD-L1 and/or PD-L2. PD-1 (programmed death 1) is also referred to in the art as “programmed cell death 1,” “PDCD1,” “CD279,” and “SLEB2.” An exemplary human PD-1 is shown in UniProtKB/Swiss-Prot Accession No. Q15116. In some instances, the PD-1 binding antagonist is a molecule that inhibits the binding of PD-1 to one or more of its binding partners. In a specific aspect, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1 and/or PD-L2. For example, PD-1 binding antagonists include anti-PD-1 antibodies, antigen-binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides, and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of PD-1 with PD-L1 and/or PD-L2. In one instance, a PD-1 binding antagonist reduces the negative co-stimulatory signal mediated by or through cell surface proteins expressed on T lymphocytes mediated signaling through PD-1 so as to render a dysfunctional T-cell less dysfunctional (e.g., enhancing effector responses to antigen recognition). In some instances, the PD-1 binding antagonist binds to PD-1. In some instances, the PD-1 binding antagonist is an anti-PD-1 antibody (e.g., an anti-PD-1 antagonist antibody). Exemplary anti-PD-1 antagonist antibodies include nivolumab, pembrolizumab, MEDI-0680, PDR001 (spartalizumab), REGN2810 (cemiplimab), BGB-108, prologlimab, camrelizumab, sintilimab, tislelizumab, toripalimab, dostarlimab, retifanlimab, sasanlimab, penpulimab, CS1003, HLX10, SCT-110A, zimberelimab, balstilimab, genolizumab, BI 754091, cetrelimab, YBL-006, BAT1306, HX008, budigalimab, AMG 404, CX-188, JTX-4014, 609A, Sym021, LZM009, F520, SG001, AM0001, ENUM 244C8, ENUM 388D4, STI-1110, AK-103, and hAb21. In a specific aspect, a PD-1 binding antagonist is MDX-1106 (nivolumab). In another specific aspect, a PD-1 binding antagonist is MK-3475 (pembrolizumab). In another specific aspect, a PD-1 binding antagonist is a PD-L2 Fc fusion protein, e.g., AMP-224. In another specific aspect, a PD-1 binding antagonist is MED1-0680. In another specific aspect, a PD-1 binding antagonist is PDR001 (spartalizumab). In another specific aspect, a PD-1 binding antagonist is REGN2810 (cemiplimab). In another specific aspect, a PD-1 binding antagonist is BGB-108. In another specific

aspect, a PD-1 binding antagonist is prolgolimab. In another specific aspect, a PD-1 binding antagonist is camrelizumab. In another specific aspect, a PD-1 binding antagonist is sintilimab. In another specific aspect, a PD-1 binding antagonist is tislelizumab. In another specific aspect, a PD-1 binding antagonist is toripalimab. Other additional exemplary PD-1 binding antagonists include BION-004, CB201, AUNP-012, ADG104, and LBL-006.

[0203] The term “PD-L2 binding antagonist” refers to a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-L2 with either one or more of its binding partners, such as PD-1. PD-L2 (programmed death ligand 2) is also referred to in the art as “programmed cell death 1 ligand 2,” “PDCD1LG2,” “CD273,” “B7-DC,” “Btdc,” and “PDL2.” An exemplary human PD-L2 is shown in UniProtKB/Swiss-Prot Accession No. Q9BQ51. In some instances, a PD-L2 binding antagonist is a molecule that inhibits the binding of PD-L2 to one or more of its binding partners. In a specific aspect, the PD-L2 binding antagonist inhibits binding of PD-L2 to PD-1. Exemplary PD-L2 antagonists include anti-PD-L2 antibodies, antigen binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of PD-L2 with either one or more of its binding partners, such as PD-1. In one aspect, a PD-L2 binding antagonist reduces the negative co-stimulatory signal mediated by or through cell surface proteins expressed on T lymphocytes mediated signaling through PD-L2 so as render a dysfunctional T-cell less dysfunctional (e.g., enhancing effector responses to antigen recognition). In some aspects, the PD-L2 binding antagonist binds to PD-L2. In some aspects, a PD-L2 binding antagonist is an immunoadhesin. In other aspects, a PD-L2 binding antagonist is an anti-PD-L2 antagonist antibody.

[0204] The term “protein,” as used herein, refers to any native protein from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed protein as well as any form of the protein that results from processing in the cell. The term also encompasses naturally occurring variants of the protein, e.g., splice variants or allelic variants.

[0205] “Percent (%) amino acid 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 for the purposes of the alignment. 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, Clustal W, Megalign (DNASTAR) software or the FASTA program package. 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. Alternatively, the percent identity values can be generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence com-

parison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087 and is described in WO 2001/007611.

[0206] Unless otherwise indicated, for purposes herein, percent amino acid sequence identity values are generated using the ggsearch program of the FASTA package version 36.3.8c or later with a BLOSUM50 comparison matrix. The FASTA program package was authored by W. R. Pearson and D. J. Lipman (1988), “Improved Tools for Biological Sequence Analysis”, PNAS 85:2444-2448; W. R. Pearson (1996) “Effective protein sequence comparison” Meth. Enzymol. 266:227-258; and Pearson et. al. (1997) Genomics 46:24-36 and is publicly available from www.fasta.bioch.virginia.edu/fasta_www2/fasta_down.shtml or www.ebi.ac.uk/Tools/ss/s/fasta. Alternatively, a public server accessible at fasta.bioch.virginia.edu/fasta_www2/index.cgi can be used to compare the sequences, using the ggsearch (global protein: protein) program and default options (BLOSUM50; open:-10; ext:-2; Ktup=2) to ensure a global, rather than local, alignment is performed. Percent amino acid identity is given in the output alignment header.

[0207] The term “pharmaceutical formulation” refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered.

[0208] A “pharmaceutically acceptable carrier” refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

[0209] By “radiation therapy” is meant the use of directed gamma rays or beta rays to induce sufficient damage to a cell so as to limit its ability to function normally or to destroy the cell altogether. It will be appreciated that there will be many ways known in the art to determine the dosage and duration of treatment. Typical treatments are given as a one-time administration and typical dosages range from 10 to 200 units (Grays) per day.

[0210] As used herein, “treatment” (and grammatical variations thereof such as “treat” or “treating”) refers to clinical intervention in an attempt to alter the natural course of the individual being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some aspects, antibodies disclosed herein (e.g., anti-FcRH5/anti-CD3 TDBs disclosed herein) and/or lenalidomide are used to delay development of a disease or to slow the progression of a disease.

[0211] By “reduce” or “inhibit” is meant the ability to cause an overall decrease, for example, of 20% or greater, of 50% or greater, or of 75%, 85%, 90%, 95%, or greater. In certain aspects, reduce or inhibit can refer to the effector function of an antibody that is mediated by the antibody Fc region, such effector functions specifically including complement-dependent cytotoxicity (CDC), antibody-de-

pendent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP).

[0212] According to the invention, the term “vaccine” relates to a pharmaceutical preparation (pharmaceutical composition) or product that upon administration induces an immune response, in particular a cellular immune response, which recognizes and attacks a pathogen or a diseased cell such as a cancer cell. A vaccine may be used for the prevention or treatment of a disease. A vaccine may be a cancer vaccine. A “cancer vaccine” as used herein is a composition that stimulates an immune response in a subject against a cancer. Cancer vaccines typically consist of a source of cancer-associated material or cells (antigen) that may be autologous (from self) or allogenic (from others) to the subject, along with other components (e.g., adjuvants) to further stimulate and boost the immune response against the antigen. Cancer vaccines can result in stimulating the immune system of the subject to produce antibodies to one or several specific antigens, and/or to produce killer T cells to attack cancer cells that have those antigens.

[0213] As used herein, “administering” is meant a method of giving a dosage of a compound (e.g., an anti-FcRH5/anti-CD3 TDB of the invention (e.g., cevostamab) or lenalidomide) to a subject. In some aspects, the compositions utilized in the methods herein are administered intravenously. The compositions utilized in the methods described herein can be administered, for example, intramuscularly, intravenously, intradermally, percutaneously, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intranasally, intravitreally, intravaginally, intrarectally, topically, intratumorally, peritoneally, subcutaneously, subconjunctivally, intravesicularily, mucosally, intrapericardially, intraumbilically, intraocularly, orally, topically, locally, by inhalation, by injection, by infusion, by continuous infusion, by localized perfusion bathing target cells directly, by catheter, by lavage, in creams, or in lipid compositions. The method of administration can vary depending on various factors (e.g., the compound or composition being administered and the severity of the condition, disease, or disorder being treated).

[0214] “CD38” as used herein refers to a CD38 glycoprotein found on the surface of many immune cells, including CD4+, CD8+, B lymphocytes, and natural killer (NK) cells, and includes any native CD38 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. CD38 is expressed at a higher level and more uniformly on myeloma cells as compared to normal lymphoid and myeloid cells. The term encompasses “full-length,” unprocessed CD38, as well as any form of CD38 that results from processing in the cell. The term also encompasses naturally occurring variants of CD38, e.g., splice variants or allelic variants. CD38 is also referred to in the art as cluster of differentiation 38, ADP-ribosyl cyclase 1, cADPr hydrolase 1, and cyclic ADP-ribose hydrolase 1. CD38 is encoded by the CD38 gene. The nucleic acid sequence of an exemplary human CD38 is shown under NCBI Reference Sequence: NM_001775.4 or in SEQ ID NO: 33. The amino acid sequence of an exemplary human CD38 protein encoded by CD38 is shown under UniProt Accession No. P28907 or in SEQ ID NO: 34.

[0215] The term “anti-CD38 antibody” encompasses all antibodies that bind CD38 with sufficient affinity such that

the antibody is useful as a therapeutic agent in targeting a cell expressing the antigen, and does not significantly cross-react with other proteins such as a negative control protein in the assays described below. For example, an anti-CD38 antibody may bind to CD38 on the surface of a MM cell and mediate cell lysis through the activation of complement-dependent cytotoxicity, ADCC, antibody-dependent cellular phagocytosis (ADCP), and apoptosis mediated by Fc cross-linking, leading to the depletion of malignant cells and reduction of the overall cancer burden. An anti-CD38 antibody may also modulate CD38 enzyme activity through inhibition of ribosyl cyclase enzyme activity and stimulation of the cyclic adenosine diphosphate ribose (cADPR) hydrolase activity of CD38. In certain aspects, an anti-CD38 antibody that binds to CD38 has a dissociation constant (K_D) of $\leq 1 \mu\text{M}$, $\leq 100 \text{nM}$, $\leq 10 \text{nM}$, $\leq 1 \text{nM}$, $\leq 0.1 \text{nM}$, or $\leq 0.01 \text{nM}$ (e.g., 10^{-8} M or less, e.g., from 10^{-8} M to 10^{-13} M , e.g., from 10^{-9} M to 10^{-13} M). In certain aspects, the anti-CD38 antibody may bind to both human CD38 and chimpanzee CD38. Anti-CD38 antibodies also include anti-CD38 antagonist antibodies. Bispecific antibodies wherein one arm of the antibody binds CD38 are also contemplated. Also encompassed by this definition of anti-CD38 antibody are functional fragments of the preceding antibodies. Examples of antibodies which bind CD38 include: daratumumab (DARZALEX®) (U.S. Pat. No. 7,829,673 and U.S. Pub. No: 20160067205 A1); “MOR202” (U.S. Pat. No. 8,263,746); and isatuximab (SAR-650984).

II. Therapeutic Methods and Compositions for Use

[0216] The invention is based, in part, on methods of treating a subject having cancer (e.g., multiple myeloma (MM) (e.g., MM with a high-risk cytogenetic feature)) with anti-fragment crystallizable receptor-like 5 (FcRH5)/anti-cluster of differentiation 3 (CD3) bispecific antibodies and lenalidomide, e.g., using fractionated, dose-escalation dosing regimens as disclosed herein.

[0217] Currently, there is no curative treatment for MM, and almost all patients will eventually relapse. Lenalidomide is currently the only drug approved as maintenance treatment after autologous stem cell transplantation (ASCT) to delay relapse and extend survival. To date, maintenance treatment is usually given as monotherapy, and patients with cytogenetic low-risk features derive survival benefit. However, patients with cytogenetic high-risk features remain a high-unmet medical need with a very poor survival benefit from single agent maintenance and a hazard ratios for death between 6 and 15 times higher than patients in the low-risk category. In a high-risk population, double agent maintenance, as described herein with cevostamab and lenalidomide, is expected to improve and deepen responses, thereby increasing survival while maintaining quality of life.

A. Dosing Regimens

i. Dosing Regimens for Treatment of a Cancer with a High-Risk Cytogenetic Feature

[0218] The present disclosure provides methods and compositions for treatment of a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM))) with a high-risk cytogenetic feature.

[0219] For example, provided herein is a method of treating a subject having a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM))) with a

high-risk cytogenetic feature, the method comprising administering to the subject (i) a bispecific antibody that binds to fragment crystallizable receptor-like 5 (FcRH5) and cluster of differentiation 3 (CD3) and (ii) lenalidomide.

[0220] In another example, provided herein is a bispecific antibody that binds to FcRH5 and CD3 for use in treatment of a subject having a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM))) with a high-risk cytogenetic feature, the treatment comprising administration of the bispecific antibody and lenalidomide to the subject.

[0221] In some examples, the subject has experienced a partial response (PR) or better after induction therapy.

[0222] In some examples, the subject has undergone autologous stem cell transplantation (ASCT) within 100 days (e.g., within 100 days, within 95 days, within 90 days, within 85 days, within 80 days, within 75 days, within 70 days, within 65 days, within 60 days, within 55 days, within 50 days, within 45 days, within 40 days, within 35 days, within 30 days, within 25 days, within 20 days, within 15 days, within 10 days, within 5 days, within 4 days, within 3 days, within 2 days, or within 1 day) of the onset of the method or treatment (e.g., the first administration of the bispecific antibody) and/or has an absence of progressive disease.

[0223] In some examples, the bispecific antibody and lenalidomide are administered to the patient as a post-transplant maintenance therapy.

[0224] The patient may have any suitable high-risk cytogenetic feature or combination thereof. In some examples, the high-risk cytogenetic feature comprises one or more of the following: translocation events t(4;14) or t(14;16), del(17p), or 1q gain.

[0225] In some examples, the subject harbored the high-risk cytogenetic feature at the time of diagnosis of the cancer (e.g., the hematologic cancer (e.g., the MM)).

[0226] In some examples, the bispecific antibody and the lenalidomide are administered to the subject in a dosing regimen comprising: (i) a first phase comprising one or more dosing cycles, wherein the first phase comprises administering the bispecific antibody to the subject every week (Q1W), every two weeks (Q2W), every three weeks (Q3W), or every four weeks (Q4W); and (ii) a second phase comprising one or more dosing cycles, wherein the second phase comprises administering the bispecific antibody to the subject every week (Q1W), every two weeks (Q2W), every three weeks (Q3W), or every four weeks (Q4W).

[0227] In one particular example, the bispecific antibody and the lenalidomide are administered to the subject in a dosing regimen comprising: (i) a first phase comprising one or more dosing cycles, wherein the first phase comprises administering the bispecific antibody to the subject every two weeks (Q2W); and (ii) a second phase comprising one or more dosing cycles, wherein the second phase comprises administering the bispecific antibody to the subject every four weeks (Q4W).

[0228] Each dosing cycle of the first phase and/or the second phase may have any suitable length. In some examples, each dosing cycle of the first phase and/or the second phase is a 28-day dosing cycle. However, in other examples, each dosing cycle of the first phase and/or the second phase may be a 7-day dosing cycle, a 14-day dosing cycle, or a 21-day dosing cycle. It is to be understood that the dosing cycles need not all have the same length.

[0229] In some examples, the method or treatment further comprising a pre-phase, prior to the first phase, comprising one or more dosing cycles, wherein the pre-phase comprises administering the bispecific antibody to the subject every week (QW), every two weeks (Q2W), every three weeks (Q3W), or every four weeks (Q4W).

[0230] In one particular, the method or treatment further comprising a pre-phase, prior to the first phase, comprising one or more dosing cycles, wherein the pre-phase comprises administering the bispecific antibody to the subject every week (QW).

[0231] Each dosing cycle of the pre-phase may have any suitable length. In some examples, each dosing cycle of the pre-phase is a 28-day dosing cycle. However, in other examples, each dosing cycle of the pre-phase may be a 7-day dosing cycle, a 14-day dosing cycle, or a 21-day dosing cycle. It is to be understood that the dosing cycles need not all have the same length.

[0232] The pre-phase may include any suitable number of dosing cycles, e.g., one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, or more dosing cycles.

[0233] In a particular example, the pre-phase comprises one dosing cycle (C1).

[0234] The pre-phase may comprise administering the bispecific antibody to the subject on any suitable day(s) of a dosing cycle (e.g., the C1), e.g., Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, Day 9, Day 10, Day 11, Day 12, Day 13, Day 14, Day 15, Day 16, Day 17, Day 18, Day 19, Day 20, Day 21, Day 22, Day 23, Day 24, Day 25, Day 26, Day 27, and/or Day 28 of a dosing cycle.

[0235] In one particular example, the pre-phase comprises administering the bispecific antibody to the subject on Days 1, 8, and 15 of the C1. In another example, the pre-phase comprises administering the bispecific antibody to the subject on Days 1, 2, and 15 of the C1.

[0236] In some examples, a target dose of the bispecific antibody is administered to the subject for each administration in the pre-phase. In other words, the pre-phase may not utilize step-up dosing.

[0237] In other examples, the pre-phase comprises administering a first step-up dose of the bispecific antibody to the subject. In some examples, the pre-phase comprises a single step-up dose of the bispecific antibody. Any of the single step-up dosing regimens described below in Subsection II may be used.

[0238] The first step-up dose may be administered to the subject on any suitable day(s) of a dosing cycle (e.g., the C1), e.g., Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, Day 9, Day 10, Day 11, Day 12, Day 13, Day 14, Day 15, Day 16, Day 17, Day 18, Day 19, Day 20, Day 21, Day 22, Day 23, Day 24, Day 25, Day 26, Day 27, and/or Day 28 of a dosing cycle.

[0239] In one particular example, the first step-up dose is administered to the subject on Day 1 of the C1. In a single step-up dosing regimen, a target dose may be administered on any suitable day following the first step-up dose, e.g., on Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, Day 9, Day 10, Day 11, Day 12, Day 13, Day 14, Day 15, Day 16, Day 17, Day 18, Day 19, Day 20, Day 21, Day 22, Day 23, Day 24, Day 25, Day 26, Day 27, and/or Day 28 of a dosing cycle (e.g., the C1). In one particular example, a target dose is administered to the subject on Days 8 and 15 of the C1.

[0240] In some examples, the pre-phase comprises administering a first step-up dose and a second step-up dose of the bispecific antibody to the subject. Any of the double step-up dosing regimens described below in Subsection III may be used.

[0241] The first step-up dose and/or the second step-up dose may be administered to the subject on any suitable day of a dosing cycle (e.g., the C1), e.g., Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, Day 9, Day 10, Day 11, Day 12, Day 13, Day 14, Day 15, Day 16, Day 17, Day 18, Day 19, Day 20, Day 21, Day 22, Day 23, Day 24, Day 25, Day 26, Day 27, and/or Day 28 of a dosing cycle.

[0242] In one particular example, the first step-up dose is administered to the subject on Day 1 of C1 and the second step-up dose is administered to the subject on Day 8 of the C1.

[0243] In a double step-up dosing regimen, a target dose may be administered on any suitable day following the second step-up dose, e.g., on Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, Day 9, Day 10, Day 11, Day 12, Day 13, Day 14, Day 15, Day 16, Day 17, Day 18, Day 19, Day 20, Day 21, Day 22, Day 23, Day 24, Day 25, Day 26, Day 27, and/or Day 28 of a dosing cycle. In one particular example, a target dose is administered to the subject on Day 15 of the C1.

[0244] Any suitable dose may be used for the first step-up dose, including any of the dosages described below in Subsections II and III. In some examples, the first step-up dose is 3.6 mg.

[0245] Any suitable dose may be used for the first step-up dose, including any of the dosages described below in Subsection III. In some examples, the first step-up dose is 0.3 mg and the second step-up dose is 3.6 mg. In other examples, the first step-up dose is 0.3 mg and the second step-up dose is 3.3 mg.

[0246] The first phase may comprise any suitable number of dosing cycles (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more dosing cycles). In some examples, the first phase comprises at least two dosing cycles, at least three dosing cycles, at least four dosing cycles, or at least five dosing cycles. In some examples, the first phase consists of five dosing cycles.

[0247] In some examples, the first phase comprises a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), and a fifth dosing cycle (C5).

[0248] In some examples, the first phase comprises administering the bispecific antibody to the subject on Days 1 and 15 of the C1, the C2, the C3, the C4, and/or the C5.

[0249] In some examples, a target dose of the bispecific antibody is administered to the subject for each administration during the first phase. Any suitable target dose may be used, including any dosage described below in Subsection II and/or Subsection III. In some examples, the target dose is between 20 mg to 600 mg (e.g., between 30 mg to 500 mg, 40 mg to 400 mg, 60 mg to 350 mg, 80 mg to 300 mg, 100 mg to 200 mg, or 140 mg to 180 mg, e.g., 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 320, 340, 360, 380, 400, 420, 440, 460, 480, 500, 520, 540, 560, 580, or 600 mg). In some aspects, the C1D3 is between 80 mg to 300 mg. In some aspects, the target dose is about 90 mg. In some aspects, the target dose is about 132 mg. In some target dose, the C1D3 is about 160 mg. In some target dose, the C1D3 is about 198 mg.

[0250] The second phase may comprise any suitable number of dosing cycles (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more dosing cycles). In some examples, the second phase comprises at least two dosing cycles, at least three dosing cycles, at least four dosing cycles, at least five dosing cycles, at least six dosing cycles, or at least seven dosing cycles. In some examples, the second phase consists of seven dosing cycles.

[0251] In some examples, the second phase comprises a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), a fifth dosing cycle (C5), a sixth dosing cycle (C6), and a seventh dosing cycle (C7).

[0252] In some examples, the second phase comprises administering the bispecific antibody to the subject on Day 1 of the C1, the C2, the C3, the C4, the C5, the C6, and/or the C7.

[0253] In some examples, a target dose of the bispecific antibody is administered to the subject for each administration during the second phase. Any suitable target dose may be used, including any dosage described below in Subsection II and/or Subsection III. In some examples, the target dose is between 20 mg to 600 mg (e.g., between 30 mg to 500 mg, 40 mg to 400 mg, 60 mg to 350 mg, 80 mg to 300 mg, 100 mg to 200 mg, or 140 mg to 180 mg, e.g., 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 320, 340, 360, 380, 400, 420, 440, 460, 480, 500, 520, 540, 560, 580, or 600 mg). In some aspects, the C1D3 is between 80 mg to 300 mg. In some aspects, the target dose is about 90 mg. In some aspects, the target dose is about 132 mg. In some target dose, the C1D3 is about 160 mg. In some target dose, the C1D3 is about 198 mg.

[0254] In some examples, the target dose is between 90 mg to 198 mg, inclusive. In some examples, the target dose is 90 mg. In some examples, the target dose is 132 mg. In some examples, the target dose is 160 mg.

[0255] The bispecific antibody may be administered by any suitable administration route. In some examples, the bispecific antibody is administered to the subject intravenously. In other examples, the bispecific antibody is administered to the subject subcutaneously.

[0256] The lenalidomide may be administered on any suitable day of a dosing cycle, e.g., on Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, Day 9, Day 10, Day 11, Day 12, Day 13, Day 14, Day 15, Day 16, Day 17, Day 18, Day 19, Day 20, Day 21, Day 22, Day 23, Day 24, Day 25, Day 26, Day 27, and/or Day 28 of a dosing cycle. In a particular example, the lenalidomide is administered to the subject on Days 1-21 of each dosing cycle in the first phase and/or the second phase. In some examples, the lenalidomide is administered to the subject on Days 1-21 of each dosing cycle in the pre-phase.

[0257] Any suitable dosage of lenalidomide may be used (e.g., about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, or about 30 mg). In some examples, the lenalidomide is administered to the subject at a dosage of about 10 mg to about 20 mg. In some examples, the lenalidomide is administered to the subject at a dosage of 10 mg to 20 mg.

[0258] In some examples, the lenalidomide is administered to the subject at a dosage of about 10 mg. In some examples, the lenalidomide is administered to the subject at a dosage of 10 mg. In other examples, the lenalidomide is administered to the subject at a dosage of about 15 mg. In other examples, the lenalidomide is administered to the subject at a dosage of 15 mg. For example, the lenalidomide may be administered at a dose of 15 mg after three cycles (e.g., the first three cycles may comprise administering lenalidomide at a dose of 10 mg, and then the dosage may be increased to 15 mg, e.g., per the clinician's discretion).

[0259] The lenalidomide may be administered by any suitable administration route. In some examples, the lenalidomide is administered to the subject orally.

[0260] In some examples, the method or treatment further comprises administering a corticosteroid to the subject. Any suitable corticosteroid may be used, e.g., dexamethasone or methylprednisolone.

[0261] In some examples, the method or treatment further comprises administering a corticosteroid to the subject during the first phase and/or the second phase.

[0262] The corticosteroid may be administered on any suitable day during a dosing cycle in the first phase and/or the second phase, e.g., on Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, Day 9, Day 10, Day 11, Day 12, Day 13, Day 14, Day 15, Day 16, Day 17, Day 18, Day 19, Day 20, Day 21, Day 22, Day 23, Day 24, Day 25, Day 26, Day 27, and/or Day 28 of a dosing cycle. The corticosteroid may be administered on the same day as the bispecific antibody or on a different day from the bispecific antibody (e.g., one or more days before or after administration of the bispecific antibody). In some examples, the corticosteroid is administered to the subject during the first phase on Days 1 and 15 of the C1 of the first phase.

[0263] In some examples, the corticosteroid is administered to the subject if the subject experienced a cytokine release syndrome (CRS) with the prior dose. In some examples, the corticosteroid is administered to the subject in the C2, the C3, the C4, and/or the C5 of the first phase if the subject experienced a CRS event with the prior dose.

[0264] In some examples, the corticosteroid is administered to the subject in the C1, the C2, the C3, the C4, the C5, the C6, and/or the C7 of the second phase if the subject experienced a CRS event with the prior dose.

[0265] In some examples, the method or treatment further comprises administering a corticosteroid to the subject during the pre-phase.

[0266] The corticosteroid may be administered on any suitable day during a dosing cycle in the pre-phase, e.g., on Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, Day 9, Day 10, Day 11, Day 12, Day 13, Day 14, Day 15, Day 16, Day 17, Day 18, Day 19, Day 20, Day 21, Day 22, Day 23, Day 24, Day 25, Day 26, Day 27, and/or Day 28 of a dosing cycle. In some examples, the corticosteroid is administered to the subject during the pre-phase on Days 1, 8, and 15 of the C1.

[0267] The corticosteroid may be administered by any suitable administration route. In some examples, the corticosteroid is administered to the subject intravenously or orally. In some examples, the corticosteroid is administered to the subject intravenously.

[0268] In some examples, the corticosteroid is administered to the subject intravenously prior to the administration of the bispecific antibody.

[0269] The corticosteroid may be administered any suitable amount of time prior to the administration of the bispecific antibody, e.g., about 1 min, 5 min, 10 min, 15 min, 20 min, 25 min, 30 min, 35 min, 40 min, 45 min, 50 min, 55 min, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, or 24 hours prior to the administration of the bispecific antibody. In some examples, the corticosteroid is administered to the subject intravenously about 1 hour prior to the administration of the bispecific antibody.

[0270] In some examples, the corticosteroid is dexamethasone or methylprednisolone.

[0271] In some examples, the corticosteroid is dexamethasone.

[0272] The dexamethasone may be administered at any suitable dosage, e.g., from 1 mg to 100 mg. In some examples, the dexamethasone is administered to the subject at a dosage of about 20 mg.

[0273] The methylprednisolone may be administered at any suitable dose, e.g., from 1 mg to 400 mg. In some examples, the methylprednisolone is administered to the subject at a dosage of about 80 mg.

[0274] Any suitable bispecific antibody may be used, e.g., any bispecific antibody disclosed herein (e.g., in Section H below).

[0275] In some examples, the bispecific antibody is cevostamab.

[0276] In some examples, the bispecific antibody and the lenalidomide are administered to the subject concurrently with one or more additional therapeutic agents. Any suitable additional therapeutic agent(s) may be used, including any disclosed herein.

[0277] In some examples, the bispecific antibody and/or the lenalidomide are administered to the subject prior to the administration of one or more additional therapeutic agents.

[0278] In some examples, the bispecific antibody/or and the lenalidomide is administered to the subject subsequent to the administration of one or more additional therapeutic agents.

[0279] In some examples, the one or more additional therapeutic agents comprise an effective amount of tocilizumab.

[0280] In some examples, the subject has a CRS event, and the method further comprises treating the symptoms of the CRS event while suspending treatment with the bispecific antibody.

[0281] In some examples, the method or treatment further comprises administering to the subject an effective amount of tocilizumab to treat the CRS event.

[0282] In some examples, the CRS event does not resolve or worsens within 24 hours of treating the symptoms of the CRS event, the method further comprising administering to the subject one or more additional doses of tocilizumab to manage the CRS event.

[0283] In some examples, tocilizumab is administered to the subject by intravenous infusion.

[0284] In some examples: (a) the subject weighs ≥ 30 kg, and tocilizumab is administered to the subject at a dose of 8 mg/kg; or (b) the subject weighs < 30 kg, and tocilizumab is administered to the subject at a dose of 12 mg/kg.

[0285] In some examples, tocilizumab is administered to the subject 2 hours before administration of the bispecific antibody.

[0286] In some examples, the one or more additional therapeutic agents comprise an effective amount of a B-cell maturation antigen (BCMA)-directed therapy, an additional immunomodulator (IMID), a CD38-directed therapy, or a combination of any of the foregoing.

[0287] In some examples, the one or more additional therapeutic agents comprise an effective amount of acetaminophen or paracetamol.

[0288] Any suitable dose of acetaminophen or paracetamol may be used. In some examples, acetaminophen or paracetamol is administered to the subject at a dose of between about 500 mg to about 1000 mg.

[0289] Acetaminophen or paracetamol may be administered by any suitable administration route, including any administration route disclosed herein. In some examples, acetaminophen or paracetamol is administered to the subject orally.

[0290] In some examples, the one or more additional therapeutic agents comprise an effective amount of diphenhydramine.

[0291] Any suitable dose of diphenhydramine may be used. In some examples, diphenhydramine is administered to the subject at a dose of between about 25 mg to about 50 mg.

[0292] Diphenhydramine may be administered by any suitable administration route, including any administration route disclosed herein. In some examples, diphenhydramine is administered orally to the subject.

[0293] In another example, provided herein is a method of treating a subject having a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM))) with a high-risk cytogenetic feature, the method comprising administering to the subject cevostamab and lenalidomide, wherein: (i) the subject experienced a PR or better after induction therapy; (ii) the subject has undergone ASCT within 100 days of the onset of the method and/or has an absence of progressive disease; (iii) the cevostamab and lenalidomide are administered to the patient as a post-transplant maintenance therapy; and (iv) the high-risk cytogenetic feature comprises one or more of the following: translocation events t(4;14) or t(14;16), del(17p), or 1q gain.

[0294] In another example, provided herein is cevostamab for use in treatment of a subject having a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM))) with a high-risk cytogenetic feature, the treatment comprising administration of cevostamab and lenalidomide to the subject, wherein: (i) the subject experienced a PR or better after induction therapy; (ii) the subject has undergone ASCT within 100 days of the onset of the method and/or has an absence of progressive disease; (iii) the cevostamab and lenalidomide are administered to the patient as a post-transplant maintenance therapy; and (iv) the high-risk cytogenetic feature comprises one or more of the following: translocation events t(4;14) or t(14;16), del(17p), or 1q gain.

[0295] In another example, provided herein is a method of treating a subject having a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM))) with a high-risk cytogenetic feature, the method comprising administering to the subject cevostamab and lenalidomide in a dosing regimen comprising: (i) a pre-phase comprising a 28-day dosing cycle (C1); (ii) a first phase, following the

pre-phase, comprising a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), and a fifth dosing cycle (C5), wherein each dosing cycle of the first phase is a 28-day dosing cycle; and (iii) a second phase, following the first phase, comprising a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), a fifth dosing cycle (C5), a sixth dosing cycle (C6), and a seventh dosing cycle (C7), wherein each dosing cycle of the second phase is a 28-day dosing cycle, wherein cevostamab is administered to the subject: (i) at a first step-up dose during the pre-phase on Day 1 of the C1 and as a second step-up dose during the pre-phase on Day 8 of the C1; (ii) at a target dose during the pre-phase on Day 15 of the C1; (iii) at a target dose during the first phase on Days 1 and 15 of the C1, the C2, the C3, the C4, and the C5; and (iv) at a target dose during the second phase on Day 1 of the C1, the C2, the C3, the C4, the C5, the C6, and the C7; and wherein lenalidomide is administered to the subject: (i) during the pre-phase on Days 1-21 of the C1; (ii) during the first phase on Days 1-21 of the C1, the C2, the C3, the C4, and the C5; and (iii) during the second phase on Days 1-21 of the C1, the C2, the C3, the C4, the C5, the C6, and the C7.

[0296] In another example, provided herein is cevostamab for use in treatment of a subject having a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM))) with a high-risk cytogenetic feature, the treatment comprising administering to the subject cevostamab and lenalidomide in a dosing regimen comprising: (i) a pre-phase comprising a 28-day dosing cycle (C1); (ii) a first phase, following the pre-phase, comprising a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), and a fifth dosing cycle (C5), wherein each dosing cycle of the first phase is a 28-day dosing cycle; and (iii) a second phase, following the first phase, comprising a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), a fifth dosing cycle (C5), a sixth dosing cycle (C6), and a seventh dosing cycle (C7), wherein each dosing cycle of the second phase is a 28-day dosing cycle, wherein cevostamab is administered to the subject: (i) at a first step-up dose during the pre-phase on Day 1 of the C1 and as a second step-up dose during the pre-phase on Day 8 of the C1; (ii) at a target dose during the pre-phase on Day 15 of the C1; (iii) at a target dose during the first phase on Days 1 and 15 of the C1, the C2, the C3, the C4, and the C5; and (iv) at a target dose during the second phase on Day 1 of the C1, the C2, the C3, the C4, the C5, the C6, and the C7; and wherein lenalidomide is administered to the subject: (i) during the pre-phase on Days 1-21 of the C1; (ii) during the first phase on Days 1-21 of the C1, the C2, the C3, the C4, and the C5; and (iii) during the second phase on Days 1-21 of the C1, the C2, the C3, the C4, the C5, the C6, and the C7.

[0297] In some examples: (i) the subject experienced a PR better after induction therapy; (ii) the subject has undergone ASCT within 100 days of the onset of the method and/or has an absence of progressive disease; (iii) the cevostamab and lenalidomide are administered to the patient as a post-transplant maintenance therapy; and (iv) the high-risk cytogenetic feature comprises one or more of the following: translocation events t(4;14) or t(14;16), del(17p), or 1q gain.

[0298] In some examples: (i) the first step-up dose of cevostamab is 0.3 mg; (ii) the second step-up dose of cevostamab is 3.6 mg; (iii) the target dose of cevostamab is

between 90 mg to 198 mg, inclusive; and (iv) lenalidomide is administered at a dose of 10 mg or 15 mg.

[0299] In some examples, the target dose is 90 mg.

[0300] In some examples, the target dose is 132 mg.

[0301] In some examples, the target dose is 160 mg.

ii. Single Step-Up Dosing Regimens

[0302] In some aspects, the invention provides methods of treating a subject having a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM (e.g., an MM with a high-risk cytogenetic feature)))) comprising administering to the subject a bispecific antibody that binds to FcRH5 and CD3 and lenalidomide in a single step-up dosing regimen.

[0303] In some aspects, the invention provides a method of treating a subject having an MM (e.g., MM with a high-risk cytogenetic feature) comprising administering to the subject a bispecific antibody that binds to FcRH5 and CD3 and lenalidomide in a dosing regimen comprising at least a first dosing cycle, wherein the first dosing cycle comprises a first dose (C1D1) and a second dose (C1D2) of the bispecific antibody, wherein the C1D1 is between about 0.05 mg to about 180 mg (e.g., between about 0.1 mg to about 160 mg, between about 0.5 mg to about 140 mg, between about 1 mg to about 120 mg, between about 1.5 mg to about 100 mg, between about 2.0 mg to about 80 mg, between about 2.5 mg to about 50 mg, between about 3.0 mg to about 25 mg, between about 3.0 mg to about 15 mg, between about 3.0 mg to about 10 mg, or between about 3.0 mg to about 5 mg) and the C1D2 is between about 0.15 mg to about 1000 mg (e.g., between about 0.5 mg to about 800 mg, between about 1 mg to about 700 mg, between about 5 mg to about 500 mg, between about 10 mg to about 400 mg, between about 25 mg to about 300 mg, between about 40 mg to about 200 mg, between about 50 mg to about 100 mg, between about 75 mg to about 100 mg, or between about 85 mg to about 100 mg) and the C1D2 is between about 0.15 mg to about 1000 mg (e.g., between about 0.5 mg to about 800 mg, between about 1 mg to about 700 mg, between about 5 mg to about 500 mg, between about 10 mg to about 400 mg, between about 25 mg to about 300 mg, between about 40 mg to about 200 mg, between about 50 mg to about 100 mg, between about 75 mg to about 100 mg, or between about 85 mg to about 100 mg).

[0304] In some aspects, the invention provides a method of treating a subject having a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM (e.g., an MM with a high-risk cytogenetic feature)))) comprising administering to the subject a bispecific antibody that binds to FcRH5 and CD3 and lenalidomide in a dosing regimen comprising at least a first dosing cycle and a second dosing cycle, wherein (a) the first dosing cycle comprises a first dose (C1D1; cycle 1, dose 1) and a second dose (C1D2; cycle 1, dose, 2) of the bispecific antibody, wherein the C1D1 is less than the C1D2, and wherein the C1D1 is between about 0.05 mg to about 180 mg (e.g., between about 0.1 mg to about 160 mg, between about 0.5 mg to about 140 mg, between about 1 mg to about 120 mg, between about 1.5 mg to about 100 mg, between about 2.0 mg to about 80 mg, between about 2.5 mg to about 50 mg, between about 3.0 mg to about 25 mg, between about 3.0 mg to about 15 mg, between about 3.0 mg to about 10 mg, or between about 3.0 mg to about 5 mg) and the C1D2 is between about 0.15 mg to about 1000 mg (e.g., between about 0.5 mg to about 800 mg, between about 1 mg to about 700 mg, between about 5 mg to about 500 mg, between about 10 mg to about 400 mg, between about 25 mg to about 300 mg, between about 40 mg to about 200 mg, between about 50 mg to about 100 mg, between about 75 mg to about 100 mg, or between about 85 mg to about 100 mg).

between about 25 mg to about 300 mg, between about 40 mg to about 200 mg, between about 50 mg to about 100 mg, between about 75 mg to about 100 mg, or between about 85 mg to about 100 mg); and (b) the second dosing cycle comprises a single dose (C2D1; cycle 2, dose 1) of the bispecific antibody, wherein the C2D1 is equal to or greater than the C1D2 and is between about 0.15 mg to about 1000 mg (e.g., between about 0.5 mg to about 800 mg, between about 1 mg to about 700 mg, between about 5 mg to about 500 mg, between about 10 mg to about 400 mg, between about 25 mg to about 300 mg, between about 40 mg to about 200 mg, between about 50 mg to about 100 mg, between about 75 mg to about 100 mg, or between about 85 mg to about 100 mg).

[0305] In some aspects, (a) the C1D1 is between about 0.5 mg to about 19.9 mg (e.g., between about 1 mg to about 18 mg, between about 2 mg to about 15 mg, between about 3 mg to about 10 mg, between about 3.3 mg to about 6 mg, or between about 3.4 mg to about 4 mg, e.g., about 3 mg, 3.2 mg, 3.3 mg, 3.4 mg, 3.6 mg, 3.8 mg, 4 mg, 4.2 mg, 4.4 mg, 4.6 mg, 4.8 mg, 5 mg, 5.2 mg, 5.6 mg, 5.8 mg, 6 mg, 6.2 mg, 6.4 mg, 6.6 mg, 6.8 mg, 7 mg, 7.2 mg, 7.4 mg, 7.6 mg, 7.8 mg, 8 mg, 8.2 mg, 8.4 mg, 8.6 mg, 8.8 mg, 9 mg, 9.2 mg, 9.4 mg, 9.6 mg, 9.8 mg, 10 mg, 10.2 mg, 10.4 mg, 10.6 mg, 10.8 mg, 11 mg, 11.2 mg, 11.4 mg, 11.6 mg, 11.8 mg, 12 mg, 12.2 mg, 12.4 mg, 12.6 mg, 12.8 mg, 13 mg, 13.2 mg, 13.4 mg, 13.6 mg, 13.8 mg, 14 mg, 14.2 mg, 14.4 mg, 14.6 mg, 14.8 mg, 15 mg, 15.2 mg, 15.4 mg, 15.6 mg, 15.8 mg, 16 mg, 16.2 mg, 16.4 mg, 16.6 mg, 16.8 mg, 17 mg, 18.2 mg, 18.4 mg, 18.6 mg, 18.8 mg, 19 mg, 19.2 mg, 19.4 mg, 19.6 mg, or 19.8 mg), and (b) the C1D2 is between about 20 mg to about 600 mg (e.g., between about 30 mg to 500 mg, 40 mg to 400 mg, 60 mg to 350 mg, 80 mg to 300 mg, 100 mg to 200 mg, or 140 mg to 180 mg, e.g., about 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 320, 340, 360, 380, 400, 420, 440, 460, 480, 500, 520, 540, 560, 580, or 600 mg).

[0306] In some aspects, the C1D1 is between about 1.2 mg to about 10.8 mg and the C1D2 is between about 80 mg to about 300 mg. In some aspects, the C1D1 is about 3.6 mg and the C1D2 is about 198 mg. In some aspects, the C1D1 is between 1.2 mg to 10.8 mg and the C1D2 is between 80 mg to 300 mg. In some aspects, the C1D1 is 3.6 mg and the C1D2 is 90 mg. In some aspects, the C1D1 is 3.6 mg and the C1D2 is 132 mg. In some aspects, the C1D1 is 3.6 mg and the C1D2 is 160 mg. In some aspects, the C1D1 is 3.6 mg and the C1D2 is 198 mg.

[0307] In other aspects, the C1D1 is 3.3 mg. In some aspects, the C1D1 is 3.3 mg and the C1D2 is between 90 mg to 198 mg, e.g., 90 mg, 132 mg, 160 mg, or 198 mg.

[0308] In some instances, the methods described above may include a first dosing cycle of three weeks or 21 days. In some instances, the methods may include administering to the subject the C1D1 and the C1D2 on or about Days 1 and 8, respectively, of the first dosing cycle.

iii. Double Step-Up Dosing Regimens

[0309] In other aspects, the invention provides methods of treating a subject having a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM (e.g., an MM with a high-risk cytogenetic feature)))) comprising administering to the subject a bispecific antibody that binds to FcRH5 and CD3 in a double step-up dosing regimen.

[0310] In some aspects, the disclosure features a method of treating a subject having a cancer (e.g., an MM (e.g., MM

with a high-risk cytogenetic feature)) comprising administering to the subject a bispecific antibody that binds to FcRH5 and CD3 and lenalidomide in a dosing regimen comprising at least a first dosing cycle, wherein the first dosing cycle comprises a first dose (C1D1), a second dose (C1D2), and a third dose (C1D3) of the bispecific antibody, wherein the C1D1 is between about 0.2 mg to about 0.4 mg (e.g., is about 0.20 mg, 0.21 mg, 0.22 mg, 0.23 mg, 0.24 mg, 0.25 mg, 0.26 mg, 0.27 mg, 0.28 mg, 0.29 mg, 0.30 mg, 0.31 mg, 0.32 mg, 0.33 mg, 0.34 mg, 0.35 mg, 0.36 mg, 0.37 mg, 0.38 mg, 0.39 mg, or 0.40 mg); the C1D2 is greater than the C1D1, and the C1D3 is greater than the C1D2. In some aspects, the C1D1 is about 0.3 mg.

[0311] In some aspects, the C1D1 is between 0.2 mg to and 0.4 mg (e.g., is 0.20 mg, 0.21 mg, 0.22 mg, 0.23 mg, 0.24 mg, 0.25 mg, 0.26 mg, 0.27 mg, 0.28 mg, 0.29 mg, 0.30 mg, 0.31 mg, 0.32 mg, 0.33 mg, 0.34 mg, 0.35 mg, 0.36 mg, 0.37 mg, 0.38 mg, 0.39 mg, or 0.40 mg). In some aspects, the disclosure provides a method of treating a subject having a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM (e.g., an MM with a high-risk cytogenetic feature)))) comprising administering to the subject a bispecific antibody that binds to FcRH5 and CD3 and lenalidomide in a dosing regimen comprising at least a first dosing cycle, wherein the first dosing cycle comprises a first dose (C1D1), a second dose (C1D2), and a third dose (C1D3) of the bispecific antibody, wherein the C1D1 is between about 0.01 mg to about 2.9 mg, the C1D2 is between about 3 mg to about 19.9 mg, and the C1D3 is between about 20 mg to about 600 mg.

[0312] In some aspects, the invention provides a method of treating a subject having a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM (e.g., an MM with a high-risk cytogenetic feature)))) comprising administering to the subject a bispecific antibody that binds to FcRH5 and CD3 and lenalidomide in a dosing regimen comprising at least a first dosing cycle and a second dosing cycle, wherein (a) the first dosing cycle comprises a first dose (C1D1), a second dose (C1D2), and a third dose (C1D3) of the bispecific antibody, wherein the C1D1 and the C1D2 are each less than the C1D3, and wherein the C1D1 is between about 0.01 mg to about 2.9 mg, the C1D2 is between about 3 mg to about 19.9 mg, and the C1D3 is between about 20 mg to about 600 mg; and (b) the second dosing cycle comprises a single dose (C2D1) of the bispecific antibody, wherein the C2D1 is equal to or greater than the C1D3 and is between about 20 mg to about 600 mg.

[0313] In some aspects, the C1D1 is between about 0.05 mg to about 2.5 mg, about 0.1 mg to about 2 mg, about 0.2 mg to about 1 mg, or about 0.2 mg to about 0.4 mg (e.g., about 0.01 mg, 0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.9 mg, 1 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, 1.6 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2 mg, 2.1 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.5 mg, 2.6 mg, 2.7 mg, 2.8 mg, or 2.9 mg). In some aspects, the C1D1 is about 0.3 mg.

[0314] In some aspects, the C1D1 is between 0.05 mg to 2.5 mg, 0.1 mg to 2 mg, 0.2 mg to 1 mg, or 0.2 mg to 0.4 mg (e.g., 0.01 mg, 0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.9 mg, 1 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, 1.6 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2 mg, 2.1 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.5 mg, 2.6 mg, 2.7 mg, 2.8 mg, or 2.9 mg). In some aspects, the C1D1 is 0.3 mg.

[0315] In some aspects, the C1D2 is between about 3 mg to about 19.9 mg (e.g., between 3 mg to about 18 mg,

between about 3.1 mg to about 15 mg, between about 3.2 mg to about 10 mg, between about 3.3 mg to about 6 mg, or between about 3.4 mg to about 4 mg, e.g., about 3 mg, 3.2 mg, 3.3 mg, 3.4 mg, 3.6 mg, 3.8 mg, 4 mg, 4.2 mg, 4.4 mg, 4.6 mg, 4.8 mg, 5 mg, 5.2 mg, 5.4 mg, 5.6 mg, 5.8 mg, 6 mg, 6.2 mg, 6.4 mg, 6.6 mg, 6.8 mg, 7 mg, 7.2 mg, 7.4 mg, 7.6 mg, 7.8 mg, 8 mg, 8.2 mg, 8.4 mg, 8.6 mg, 8.8 mg, 9 mg, 9.2 mg, 9.4 mg, 9.6 mg, 9.8 mg, 10 mg, 10.2 mg, 10.4 mg, 10.6 mg, 10.8 mg, 11 mg, 11.2 mg, 11.4 mg, 11.6 mg, 11.8 mg, 12 mg, 12.2 mg, 12.4 mg, 12.6 mg, 12.8 mg, 13 mg, 13.2 mg, 13.4 mg, 13.6 mg, 13.8 mg, 14 mg, 14.2 mg, 14.4 mg, 14.6 mg, 14.8 mg, 15 mg, 15.2 mg, 15.4 mg, 15.6 mg, 15.8 mg, 16 mg, 16.2 mg, 16.4 mg, 16.6 mg, 16.8 mg, 17 mg, 18.2 mg, 18.4 mg, 18.6 mg, 18.8 mg, 19 mg, 19.2 mg, 19.4 mg, 19.6 mg, or 19.8 mg). In some aspects, the C1D2 is between about 3.2 mg to about 10 mg. In some aspects, the C1D2 is about 3.6 mg. In other aspects, the C1D2 is about 3.3 mg.

[0316] In some aspects, the C1D2 is between 3 mg to 19.9 mg (e.g., between 3 mg to 18 mg, between 3.1 mg to 15 mg, between 3.2 mg to 10 mg, between 3.3 mg to 6 mg, or between 3.4 mg to 4 mg, e.g., 3 mg, 3.2 mg, 3.3 mg, 3.4 mg, 3.6 mg, 3.8 mg, 4 mg, 4.2 mg, 4.4 mg, 4.6 mg, 4.8 mg, 5 mg, 5.2 mg, 5.4 mg, 5.6 mg, 5.8 mg, 6 mg, 6.2 mg, 6.4 mg, 6.6 mg, 6.8 mg, 7 mg, 7.2 mg, 7.4 mg, 7.6 mg, 8 mg, 8.2 mg, 8.4 mg, 8.6 mg, 8.8 mg, 9 mg, 9.2 mg, 9.4 mg, 9.6 mg, 9.8 mg, 10 mg, 10.2 mg, 10.4 mg, 10.6 mg, 10.8 mg, 11 mg, 11.2 mg, 11.4 mg, 11.6 mg, 11.8 mg, 12 mg, 12.2 mg, 12.4 mg, 12.6 mg, 12.8 mg, 13 mg, 13.2 mg, 13.4 mg, 13.6 mg, 13.8 mg, 14 mg, 14.2 mg, 14.4 mg, 14.6 mg, 14.8 mg, 15 mg, 15.2 mg, 15.4 mg, 15.6 mg, 15.8 mg, 16 mg, 16.2 mg, 16.4 mg, 16.6 mg, 16.8 mg, 17 mg, 18.2 mg, 18.4 mg, 18.6 mg, 18.8 mg, 19 mg, 19.2 mg, 19.4 mg, 19.6 mg, or 19.8 mg). In some aspects, the C1D2 is between 3.2 mg to 10 mg. In some aspects, the C1D2 is 3.6 mg. In other aspects, the C1D2 is 3.3 mg.

[0317] In some aspects, the C1D3 is between about 20 mg to about 600 mg (e.g., between about 30 mg to about 500 mg, about 40 mg to about 400 mg, about 60 mg to about 350 mg, about 80 mg to about 300 mg, about 100 mg to about 200 mg, or about 140 mg to about 180 mg, e.g., about 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 320, 340, 360, 380, 400, 420, 440, 460, 480, 500, 520, 540, 560, 580, or 600 mg). In some aspects, the C1D3 is between about 80 mg to about 300 mg. In some aspects, the C1D3 is about 90 mg. In some aspects, the C1D3 is about 132 mg. In some aspects, the C1D3 is about 160 mg. In some aspects, the C1D3 is about 198 mg.

[0318] In some aspects, the C1D3 is between 20 mg to 600 mg (e.g., between 30 mg to 500 mg, 40 mg to 400 mg, 60 mg to 350 mg, 80 mg to 300 mg, 100 mg to 200 mg, or 140 mg to 180 mg, e.g., 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 320, 340, 360, 380, 400, 420, 440, 460, 480, 500, 520, 540, 560, 580, or 600 mg). In some aspects, the C1D3 is between 80 mg to 300 mg. In some aspects, the C1D3 is about 90 mg. In some aspects, the C1D3 is about 132 mg. In some aspects, the C1D3 is about 160 mg. In some aspects, the C1D3 is about 198 mg.

[0319] In some aspects, the method comprises only a single dosing cycle (e.g., a dosing cycle comprising a C1D1, a C1D2, and a C1D3). In other aspects, the dosing regimen further comprises a second dosing cycle comprising at least a single dose (C2D1) of the bispecific antibody. In some aspects, the C2D1 is equal to or greater than the C1D3 and is between about 20 mg to about 600 mg (e.g., between

about 30 mg to about 500 mg, about 40 mg to about 400 mg, about 60 mg to about 350 mg, about 80 mg to about 300 mg, about 100 mg to about 200 mg, or about 140 mg to about 180 mg, e.g., about 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 320, 340, 360, 380, 400, 420, 440, 460, 480, 500, 520, 540, 560, 580, or 600 mg). In some aspects, the C2D1 is between about 80 mg to about 300 mg. In some aspects, the C2D1 is about 90 mg. In some aspects, the C2D1 is about 132 mg. In some aspects, the C2D1 is about 160 mg. In some aspects, the C2D1 is about 198 mg.

[0320] In some aspects, the C2D1 is between 20 mg to 600 mg (e.g., between 30 mg to 500 mg, 40 mg to 400 mg, 60 mg to 350 mg, 80 mg to 300 mg, 100 mg to 200 mg, or 140 mg to 180 mg, e.g., 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 320, 340, 360, 380, 400, 420, 440, 460, 480, 500, 520, 540, 560, 580, or 600 mg). In some aspects, the C2D1 is between 80 mg to 300 mg. In some aspects, the C2D1 is 160 mg. In some aspects, the C2D1 is 159 mg.

[0321] Alternatively, in any of the above embodiments, the C1D1 may be between about 0.01 mg to about 60 mg (e.g., between about 0.05 mg to about 50 mg, between about 0.01 mg to about 40 mg, between about 0.1 mg to about 20 mg, between about 0.1 mg to about 10 mg, between about 0.1 mg to about 5 mg, between about 0.1 mg to about 2 mg, between about 0.1 mg to about 1.5 mg, between about 0.1 mg to about 1.2 mg, between about 0.1 mg to about 0.5 mg, or between about 0.2 mg to about 0.4 mg, e.g., about 0.3 mg, e.g., 0.3 mg), the C1D2 may be between about 0.05 mg to about 180 mg (e.g., between about 0.1 mg to about 160 mg, between about 0.5 mg to about 140 mg, between about 1 mg to about 120 mg, between about 1.5 mg to about 100 mg, between about 2.0 mg to about 80 mg, between about 2.5 mg to about 50 mg, between about 3.0 mg to about 25 mg, between about 3.0 mg to about 15 mg, between about 3.0 mg to about 10 mg, between about 3.0 mg to about 5 mg, or between about 3.0 mg to about 4.0 mg, e.g., about 3.6 mg, e.g., 3.6 mg), and the C1D3 may be between about 0.15 mg to about 1000 mg (e.g., between about 0.5 mg to about 800 mg, between about 1 mg to about 700 mg, between about 5 mg to about 500 mg, between about 10 mg to about 400 mg, between about 25 mg to about 300 mg, between about 40 mg to about 200 mg, between about 50 mg to about 190 mg, between about 140 mg to about 180 mg, or between about 150 mg to about 170 mg, e.g., about 160 mg, e.g., 160 mg); and in aspects comprising a second dosing cycle, the C2D1 may be between about 0.15 mg to about 1000 mg (e.g., between about 0.5 mg to about 800 mg, between about 1 mg to about 700 mg, between about 5 mg to about 500 mg, between about 10 mg to about 400 mg, between about 25 mg to about 300 mg, between about 40 mg to about 200 mg, between about 50 mg to about 190 mg, between about 140 mg to about 180 mg, or between about 150 mg to about 170 mg, e.g., about 160 mg, e.g., 160 mg).

[0322] In some instances, the length of the first dosing cycle is four weeks or 28 days. In other instances, the length of the first dosing cycle is three weeks or 21 days. In some instances, the methods may include administering to the subject the C1D1, the C1D2, and the C1D3 on or about Days 1, 8, and 15, respectively, of the first dosing cycle.

iv. Further Dosing Cycles

[0323] In some instances, the methods described above may include a second dosing cycle of four weeks or 28 days. In other instances, the length of the first dosing cycle is one week or 7 days; two weeks or 14 days; or three weeks or 21 days. In some instances, the methods may include administering to the subject the C2D1 on or about Day 1 of the second dosing cycle.

[0324] In some instances in which the methods include at least a second dosing cycle, the methods may include one or

more additional dosing cycles. In some instances, the dosing regimen comprises 1 to 17 additional dosing cycles (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 additional dosing cycles, e.g., 1-3 additional dosing cycles, 1-5 additional dosing cycles, 3-8 additional dosing cycles, 5-10 additional dosing cycles, 8-12 additional dosing cycles, 10-15 additional dosing cycles, 12-17 additional dosing cycles, or 15-17 additional dosing cycles, i.e., the dosing regimen includes one or more of additional dosing cycle(s) C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, C15, C16, C17, C18, and C19. In some embodiments, the length of each of the one or more additional dosing cycles is 7 days, 14 days, 21 days, or 28 days. In some embodiments, the length of each of the one or more additional dosing cycles is between 5 days and 30 days, e.g., between 5 and 9 days, between 7 and 11 days, between 9 and 13 days, between 11 and 15 days, between 13 and 17 days, between 15 and 19 days, between 17 and 21 days, between 19 and 23 days, between 21 and 25 days, between 23 and 27 days, or between 25 and 30 days. In some instances, the length of each of the one or more additional dosing cycles is three weeks or 21 days. In some instances, each of the one or more additional dosing cycles comprises a single dose of the bispecific antibody. In some aspects, the dose of the bispecific antibody in the one or more additional dosing cycles is equal to the C2D1, e.g., is between about 20 mg to about 600 mg (e.g., between about 30 mg to about 500 mg, about 40 mg to about 400 mg, about 60 mg to about 350 mg, about 80 mg to about 300 mg, about 100 mg to about 200 mg, or about 140 mg to about 180 mg, e.g., about 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 320, 340, 360, 380, 400, 420, 440, 460, 480, 500, 520, 540, 560, 580, or 600 mg). In some aspects, the dose of the bispecific antibody in the one or more additional dosing cycles is about 90 mg. In some aspects, the dose of the bispecific antibody in the one or more additional dosing cycles is about 132 mg. In some aspects, the dose of the bispecific antibody in the one or more additional dosing cycles is about 160 mg. In some aspects, the dose of the bispecific antibody in the one or more additional dosing cycles is about 198 mg. In some aspects, the dose of the bispecific antibody in the one or more additional dosing cycles is equal to the C2D1, e.g., is between 20 mg to 600 mg (e.g., between 30 mg to 500 mg, 40 mg to 400 mg, 60 mg to 350 mg, 80 mg to 300 mg, 100 mg to 200 mg, or 140 mg to 180 mg, e.g., 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 320, 340, 360, 380, 400, 420, 440, 460, 480, 500, 520, 540, 560, 580, or 600 mg). In some aspects, the dose of the bispecific antibody in the one or more additional dosing cycles is 90 mg. In some aspects, the dose of the bispecific antibody in the one or more additional dosing cycles is 132 mg. In some aspects, the dose of the bispecific antibody in the one or more additional dosing cycles is 160 mg. In some aspects, the dose of the bispecific antibody in the one or more additional dosing cycles is 198 mg. In some instances, the method comprises administering to the subject the single dose of the bispecific antibody on or about Day 1 of the one or more additional dosing cycles.

[0325] In some instances, the bispecific anti-FcRH5/anti-CD3 antibody is administered to the subject as a monotherapy.

B. Combination Therapies with Additional Therapeutic Agents

[0326] In some instances, the bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide are administered to the subject with one or more additional therapeutic agents, including any additional therapeutic agents disclosed herein.

i. Anti-CD38 Antibodies

[0327] In some instances, the bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide are administered to the subject in combination with an anti-CD38 antibody. The

anti-CD38 antibody may be administered by any suitable administration route, e.g., intravenously (IV) or subcutaneously (SC) to the subject. In some aspects, the anti-CD38 antibody is daratumumab (e.g., daratumumab/rHuPH20). The daratumumab may be administered to the subject at a dose of about 900 mg to about 3600 mg (e.g., about 900 mg, about 950 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg about 1900 mg, about 1950 mg, about 2000 mg, about 2100 mg, about 2200 mg, about 2300 mg, about 2400 mg, about 2500 mg, about 2600 mg, about 2700 mg, about 2800 mg, about 2900 mg, about 3000 mg, about 3100 mg, about 3200 mg, about 3300 mg, about 3400 mg, about 3500 mg, or about 3600 mg). The daratumumab may be administered to the subject at a dose of about 1800 mg. In some aspects, the daratumumab is administered by intravenous infusion (e.g., infusion over 3-5 hours) at a dose of 16 mg/kg once every week, once every two weeks, or once every four weeks. In some aspects, the daratumumab is administered by intravenous infusion (e.g., infusion over 3-5 hours) at a dose of 16 mg/kg. In some aspects, the daratumumab is administered subcutaneously. In other aspects, the anti-CD38 antibody is isatuximab. In some aspects, the anti-CD38 antibody (e.g., daratumumab or isatuximab) is administered to the subject prior to the administration of the bispecific anti-FcRH5/anti-CD3 antibody, e.g., administered one day prior to the administration of the bispecific anti-FcRH5/anti-CD3 antibody. In some aspects, the anti-CD38 antibody (e.g., daratumumab or isatuximab) is administered to the subject concurrently with the administration of the bispecific anti-FcRH5/anti-CD3 antibody.

ii. Corticosteroids

[0328] In some instances, the bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide are administered to the subject in combination with a corticosteroid. The corticosteroid may be administered orally to the subject. The corticosteroid may be administered by any suitable administration route, e.g., intravenously or subcutaneously to the subject. Any suitable corticosteroid may be used, e.g., dexamethasone, methylprednisolone, prednisone, prednisolone, betamethasone, hydrocortisone, and the like. In some aspects, the corticosteroid is methylprednisolone. The methylprednisolone may be administered to the subject at a dose of about 80 mg. In other aspects, the corticosteroid is dexamethasone. The dexamethasone may be administered to the subject at a dose of about 20 mg. In some aspects, the corticosteroid (e.g., methylprednisolone or dexamethasone) is administered to the subject prior to the administration of the bispecific anti-FcRH5/anti-CD3 antibody and/or the lenalidomide, e.g., administered one hour prior to the administration of the bispecific anti-FcRH5/anti-CD3 antibody and/or the lenalidomide. In some aspects, the corticosteroid (e.g., methylprednisolone or dexamethasone) is administered to the subject about one day prior to the administration of the bispecific anti-FcRH5/anti-CD3 antibody and/or the lenalidomide. In some aspects, the corticosteroid (e.g., methylprednisolone or dexamethasone) is administered to the subject concurrently with the administration of the bispecific anti-FcRH5/anti-CD3 antibody and/or the lenalidomide.

iii. Immunomodulatory Drugs (IMiD)

[0329] In some instances, the bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide are administered to the subject in combination with an additional immunomodulatory drug (IMiD). The IMiD may be administered by any suitable administration route, e.g., orally to the subject. The

IMiD may be administered intravenously to the subject. The IMiD may be administered subcutaneously to the subject. In some aspects, the IMiD is pomalidomide. The pomalidomide may be administered to the subject at a dose of about 4 mg. In some aspects, the IMiD (e.g., pomalidomide) is administered to the subject prior to the administration of the bispecific anti-FcRH5/anti-CD3 antibody and/or lenalidomide, e.g., administered one hour prior to the administration of the bispecific anti-FcRH5/anti-CD3 antibody and/or lenalidomide. In some aspects, the IMiD (e.g., pomalidomide) is administered to the subject concurrently with the administration of the bispecific anti-FcRH5/anti-CD3 antibody and/or lenalidomide. In some aspects, the IMiD (e.g., pomalidomide) is administered daily between doses of the bispecific anti-FcRH5/anti-CD3 antibody and/or lenalidomide.

iv. Tocilizumab and Treatment of CRS

[0330] In one instance, the additional therapeutic agent is an effective amount of tocilizumab (ACTEMRA®). In some instances, the subject has a cytokine release syndrome (CRS) event (e.g., has a CRS event following treatment with the bispecific antibody, e.g., has a CRS event following a C1D1, a C1D2, a C1D3, a C2D1, or an additional dose of the bispecific antibody), and the method further comprises treating the symptoms of the CRS event (e.g., treating the CRS event by administering to the subject an effective amount of tocilizumab) while suspending treatment with the bispecific antibody. In some aspects, tocilizumab is administered intravenously to the subject as a single dose of about 8 mg/kg. In some aspects, the CRS event does not resolve or worsens within 24 hours of treating the symptoms of the CRS event, and the method further comprising administering to the subject one or more additional doses of tocilizumab to manage the CRS event, e.g., administering one or more additional doses of tocilizumab intravenously to the subject at a dose of about 8 mg/kg.

[0331] In some aspects, treating the symptoms of the CRS event further comprises treatment with a high-dose vasoconstrictor (e.g., norepinephrine, dopamine, phenylephrine, epinephrine, or vasopressin and norepinephrine), e.g., as described in Tables 2A and 2B.

[0332] In other instances, tocilizumab is administered as a premedication, e.g., is administered to the subject prior to the administration of the bispecific anti-FcRH5/anti-CD3 antibody. In some instances, tocilizumab is administered as a premedication in Cycle 1, e.g., is administered prior to a first dose (C1D1) of the bispecific antibody, a second dose (C1D2) of the bispecific antibody, and/or a third dose (C1D3) of the bispecific anti-FcRH5/anti-CD3 antibody. In some aspects, the tocilizumab is administered intravenously to the subject as a single dose of about 8 mg/kg.

v. CRS Symptoms and Grading

[0333] CRS may be graded according to the Modified Cytokine Release Syndrome Grading System established by Lee et al., *Blood*, 124:188-195, 2014 or Lee et al., *Biol Blood Marrow Transplant*, 25 (4): 625-638, 2019, as described in Table 2A. In addition to diagnostic criteria, recommendations on management of CRS based on its severity, including early intervention with corticosteroids and/or anti-cytokine therapy, are provided and referenced in Tables 2A and 2B.

TABLE 2A

Cytokine release syndrome grading systems		
Grade	Modified Cytokine Release Syndrome Grading System	ASTCT Consensus Grading System
Grade 1	Symptoms are not life threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise)	Temperature $\geq 38^{\circ}\text{C}$. No hypotension No hypoxia
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40%; or Hypotension responsive to fluids or low dose ^a of one vasopressor; or Grade 2 organ toxicity	Temperature $\geq 38^{\circ}\text{C}$.* with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula ^d or blow-by
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement $\geq 40\%$; or Hypotension requiring high dose ^b or multiple vasopressors; or Grade 3 organ toxicity or Grade 4 transaminitis	Temperature $\geq 38^{\circ}\text{C}$.* with hypotension requiring a vasopressor with or without vasopressin and/or ^c hypoxia requiring high-flow nasal cannula ^d , facemask, nonrebreather mask, or Venturi mask
Grade 4	Life-threatening symptoms Requirement for ventilation support or Grade 4 organ toxicity (excluding transaminitis)	Temperature $\geq 38^{\circ}\text{C}$.* with hypotension requiring multiple vasopressors (excluding vasopressin) and/or ^c hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)
Grade 5	Death	Death

Lee 2014 criteria: Lee et al., *Blood*, 124: 188-195, 2014.

[0334] ASTCT consensus grading: Lee et al., *Biol Blood Marrow Transplant*, 25 (4): 625-638, 2019.

[0335] ^a Low-dose vasopressor: single vasopressor at doses below that shown in Table 2B.

[0336] ^b High-dose vasopressor: as defined in Table 2B.

[0337] *Fever is defined as temperature $\geq 38^{\circ}\text{C}$. not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[0338] ^dCRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C ., hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[0339] ^dLow-flow nasal cannula is defined as oxygen delivered at $\leq 6\text{L}/\text{minute}$. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at $>6\text{L}/\text{minute}$.

TABLE 2B

High-dose vasopressors	
High-Dose Vasopressors (duration ≥ 3 hours)	
Pressor	Dose
Norepinephrine monotherapy	$\geq 20\text{ }\mu\text{g}/\text{min}$
Dopamine monotherapy	$\geq 10\text{ }\mu\text{g}/\text{kg}/\text{min}$
Phenylephrine monotherapy	$\geq 200\text{ }\mu\text{g}/\text{min}$
Epinephrine monotherapy	$\geq 10\text{ }\mu\text{g}/\text{min}$
If on vasopressin	Vasopressin + norepinephrine equivalent of $\geq 10\text{ }\mu\text{g}/\text{min}$ ^a
If on combination or vasopressors (not vasopressin)	Norepinephrine equivalent of $\geq 20\text{ }\mu\text{g}/\text{min}$ ^a

min = minute; VASST = Vasopressin and Septic Shock Trial.

^a VASST vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine ($\mu\text{g}/\text{min}$)] + [dopamine ($\mu\text{g}/\text{kg}/\text{min}$) + 2] + [epinephrine ($\mu\text{g}/\text{min}$)] + [phenylephrine ($\mu\text{g}/\text{min}$) + 10].

[0340] Mild to moderate presentations of CRS and/or infusion-related reaction (IRR) may include symptoms such as fever, headache, and myalgia, and may be treated symptomatically with analgesics, anti-pyretics, and antihistamines as indicated. Severe or life-threatening presentations of CRS and/or IRR, such as hypotension, tachycardia, dyspnea, or chest discomfort should be treated aggressively with supportive and resuscitative measures as indicated, including the use of high-dose corticosteroids, IV fluids, admission to intensive care unit, and other supportive measures. Severe CRS may be associated with other clinical sequelae such as disseminated intravascular coagulation, capillary leak syndrome, or macrophage activation syndrome (MAS). Standard of care for severe or life-threatening CRS resulting from immune-based therapy has not been established; case reports and recommendations using anti-cytokine therapy such as tocilizumab have been published (Teachey et al., *Blood*, 121:5154-5157, 2013; Lee et al., *Blood*, 124:188-195, 2014; Maude et al., *New Engl J Med*, 371:1507-1517, 2014).

[0341] As noted in Table 2A, even moderate presentations of CRS in subjects with extensive comorbidities should be monitored closely, with consideration given to intensive care unit admission and tocilizumab administration.

vi. Administration of Tocilizumab as a Premedication

[0342] In some aspects, an effective amount of an interleukin-6 receptor (IL-6R) antagonist (e.g., an anti-IL-6R antibody, e.g., tocilizumab (ACTEMRA®/ROACTEMRA®)) is administered as a premedication (prophylaxis), e.g., is administered to the subject prior to the administration of the bispecific antibody (e.g., administered about 2 hours prior to the administration of the bispecific antibody). Administration of tocilizumab as a premedication may reduce the frequency or severity of CRS. In some aspects, tocilizumab is administered as a premedication in Cycle 1, e.g., is administered prior to a first dose (C1D1; cycle 1, dose 1), a second dose (C1D2; cycle 1, dose, 2), and/or a third dose (C1D3; cycle 1, dose 3) of the bispecific antibody. In some aspects, the tocilizumab is administered intravenously to the subject as a single dose of about 1 mg/kg to about 15 mg/kg, e.g., about 4 mg/kg to about 10 mg/kg, e.g., about 6 mg/kg to about 10 mg/kg, e.g., about 8 mg/kg. In some aspects, the tocilizumab is administered intravenously to the subject as a single dose of about 8 mg/kg. In some aspects, the tocilizumab is administered intravenously to the subject as a single dose of about 8 mg/kg for patients weighing 30 kg or more (maximum 800 mg) and at a dose of about 12 mg/kg for patients weighing less than 30 kg. Other anti-IL-6R antibodies that could be used in combination with tocilizumab include sarilumab, vobarilizumab (ALX-0061), SA-237, and variants thereof.

[0343] For example, in one aspect, the bispecific antibody is co-administered with tocilizumab (ACTEMRA®/ROACTEMRA®), wherein the subject is first administered with tocilizumab (ACTEMRA®/ROACTEMRA®) and then separately administered with the bispecific antibody (e.g., the subject is pre-treated with tocilizumab (ACTEMRA®/ROACTEMRA®)).

[0344] In some aspects, the incidence of CRS (e.g., Grade 1 CRS, Grade 2 CRS, and/or Grade 3+ CRS) is reduced in patients who are treated with tocilizumab as a premedication relative to patients who are not treated with tocilizumab as a premedication. In some aspects, less intervention to treat CRS (e.g., less need for additional tocilizumab, IV fluids,

steroids, or O₂) is required in patients who are treated with tocilizumab as a premedication relative to patients who are not treated with tocilizumab as a premedication. In some aspects, CRS symptoms have decreased severity (e.g., are limited to fevers and rigors) in patients who are treated with tocilizumab as a premedication relative to patients who are not treated with tocilizumab as a premedication.

vii. Tocilizumab Administered to Treat CRS

[0345] In some aspects, the subject experiences a CRS event during treatment with the therapeutic bispecific antibody and an effective amount of an IL-6R antagonist (e.g., an anti-IL-6R antibody, e.g., tocilizumab (ACTEMRA®/ROACTEMRA®)) is administered to manage the CRS event.

[0346] In some aspects, the subject has a CRS event (e.g., has a CRS event following treatment with the bispecific antibody, e.g., has a CRS event following a first dose or a subsequent dose of the bispecific antibody), and the method further includes treating the symptoms of the CRS event while suspending treatment with the bispecific antibody.

[0347] In some aspects, the subject experiences a CRS event, and the method further includes administering to the subject an effective amount of an interleukin-6 receptor (IL-6R) antagonist (e.g., an anti-IL-6R antibody, e.g., tocilizumab (ACTEMRA®/ROACTEMRA®)) to manage the CRS event while suspending treatment with the bispecific antibody. In some aspects, the IL-6R antagonist (e.g., tocilizumab) is administered intravenously to the subject as a single dose of about 1 mg/kg to about 15 mg/kg, e.g., about 4 mg/kg to about 10 mg/kg, e.g., about 6 mg/kg to about 10 mg/kg, e.g., about 8 mg/kg. In some aspects, the tocilizumab is administered intravenously to the subject as a single dose of about 8 mg/kg. Other anti-IL-6R antibodies that could be used in combination with tocilizumab include sarilumab, vobarilizumab (ALX-0061), SA-237, and variants thereof.

[0348] In some aspects, the CRS event does not resolve or worsens within 24 hours of treating the symptoms of the CRS event, and the method further includes administering to the subject one or more additional doses of the IL-6R antagonist (e.g., an anti-IL-6R antibody, e.g., tocilizumab) to manage the CRS event, e.g., administering one or more additional doses of tocilizumab intravenously to the subject at a dose of about 1 mg/kg to about 15 mg/kg, e.g., about 4 mg/kg to about 10 mg/kg, e.g., about 6 mg/kg to about 10 mg/kg, e.g., about 8 mg/kg. In some aspects, the one or more additional doses of tocilizumab are administered intravenously to the subject as a single dose of about 8 mg/kg.

[0349] In some aspects, the method further includes administering to the subject an effective amount of a corticosteroid. The corticosteroid may be administered intravenously to the subject. In other examples, the corticosteroid may be administered subcutaneously to the subject. In some aspects, the corticosteroid is methylprednisolone. In some instances, the methylprednisolone is administered at a dose of about 1 mg/kg per day to about 5 mg/kg per day, e.g., about 2 mg/kg per day. In some instances, the corticosteroid is dexamethasone. In some instances, the dexamethasone is administered at a dose of about 10 mg (e.g., a single dose of about 10 mg intravenously) or at a dose of about 0.5 mg/kg/day.

[0350] The subject may be administered a corticosteroid, such as methylprednisolone or dexamethasone, if the CRS event is not managed with administration of the IL-6R antagonist (e.g., tocilizumab) alone. In some aspects, treating the symptoms of the CRS event further includes treat-

ment with a high-dose vasopressor (e.g., norepinephrine, dopamine, phenylephrine, epinephrine, or vasopressin and norepinephrine), e.g., as described in Tables 2A and Table 2B. Tables 3A and 3B further provide details about tocilizumab treatment of severe or life-threatening CRS.

viii. Management of CRS Events by Grade

[0351] Management of the CRS events may be tailored based on the grade of the CRS (Tables 2A and 3A) and the presence of comorbidities. Table 3A provides recommendations for the management of CRS syndromes by grade. Table 3B provides recommendations for the management of IRR syndromes by grade.

TABLE 3A

Recommendations for management of cytokine release syndrome (CRS)	
Event ^{a, b}	Action to Be Taken ^b
Grade 1 Fever ($\geq 38^{\circ}$ C. or 100.4° F. not attributable to any other cause)	<p>Immediate actions: If cevostamab infusion is still ongoing, interrupt infusion immediately. Call to ensure tocilizumab is readily available if needed. Provide supportive care for constitutional symptoms.^c Treat fever and neutropenia if present. Monitor fluid balance; administer IV fluids as clinically indicated. Consider hospitalization until symptoms completely resolve. In case of rapid decline in overall health or prolonged CRS (>24 hours) or in patients with significant symptoms and/or comorbidities (per investigator discretion, e.g., impaired cardiovascular function, reduced pulmonary reserve), consider administration of IV corticosteroids and tocilizumab or another anti-cytokine agent based on characterization of CRS.</p> <p>Restarting infusion: If cevostamab infusion was interrupted, wait until 30 minutes after the event has resolved before restarting the infusion at 50% of the original infusion rate. If symptoms recur, discontinue infusion for this dose.</p> <p>Next dose: Pretreat with antihistamines, antipyretics, and/or analgesics. Pretreat with IV corticosteroids (dexamethasone 20 mg (preferred) or methylprednisolone 80 mg). Consider hospitalization for next dose. Consider extending infusion time (slower infusion rate) for subsequent cycles.</p> <p>Immediate actions: Follow all Grade 1 recommendations. Hold further cevostamab treatment until symptoms completely resolved. Hospitalize patient until complete resolution of signs and symptoms. Administer tocilizumab 8 mg/kg IV^d Consider treatment with IV corticosteroids (such as methylprednisolone 2 mg/kg/day or, if neurologic symptoms are present, dexamethasone 10 mg IV every 6 hours if needed).^b Monitor cardiac and other organ function closely. Manage constitutional symptoms and organ toxicities as required. Provide hemodynamic support with IV fluid bolus 250-500 mL up to 2000 mL total (avoid fluid overload). Provide oxygen for hypoxia. Admit to ICU as appropriate. If no improvement within 8-12 hours after administration of tocilizumab, manage as a Grade 3 event: Initiate workup and assess for signs and symptoms of MAS/HLH.</p> <p>Restarting infusion: Wait until 30 minutes after the event has resolved before restarting the infusion at up to 25% of the original infusion rate. If symptoms recur, stop infusion immediately. Cevostamab should not be restarted. If hypotension or hypoxia recurs, manage as a Grade 3 event.</p> <p>Next cycle: May receive the next dose of cevostamab if symptoms resolve to Grade ≤ 1 for 3 consecutive days as follows: Consider hospitalization for at least 24 hours after the infusion. Administer cevostamab at 50% of the initial infusion rate of the previous cycle if the event occurred during or within 24 hours of the infusion.^e Pretreat with antihistamines, antipyretics, and/or analgesics.</p>
Grade 2 Fever ($\geq 38^{\circ}$ C. or 100.4° F. not attributable to any other cause) Hypotension: responds to fluids, not requiring vasopressors Hypoxia: requiring low flow nasal cannula or blow-by	<p>Immediate actions: Follow all Grade 1 recommendations. Hold further cevostamab treatment until symptoms completely resolved. Hospitalize patient until complete resolution of signs and symptoms. Administer tocilizumab 8 mg/kg IV^d Consider treatment with IV corticosteroids (such as methylprednisolone 2 mg/kg/day or, if neurologic symptoms are present, dexamethasone 10 mg IV every 6 hours if needed).^b Monitor cardiac and other organ function closely. Manage constitutional symptoms and organ toxicities as required. Provide hemodynamic support with IV fluid bolus 250-500 mL up to 2000 mL total (avoid fluid overload). Provide oxygen for hypoxia. Admit to ICU as appropriate. If no improvement within 8-12 hours after administration of tocilizumab, manage as a Grade 3 event: Initiate workup and assess for signs and symptoms of MAS/HLH.</p> <p>Restarting infusion: Wait until 30 minutes after the event has resolved before restarting the infusion at up to 25% of the original infusion rate. If symptoms recur, stop infusion immediately. Cevostamab should not be restarted. If hypotension or hypoxia recurs, manage as a Grade 3 event.</p> <p>Next cycle: May receive the next dose of cevostamab if symptoms resolve to Grade ≤ 1 for 3 consecutive days as follows: Consider hospitalization for at least 24 hours after the infusion. Administer cevostamab at 50% of the initial infusion rate of the previous cycle if the event occurred during or within 24 hours of the infusion.^e Pretreat with antihistamines, antipyretics, and/or analgesics.</p>

TABLE 3A-continued

Recommendations for management of cytokine release syndrome (CRS)		
Event ^{a, b}	Action to Be Taken ^b	
Grade 3	Pretreat with IV corticosteroids (dexamethasone 20 mg (preferred) or methylprednisolone 80 mg). Subsequent cycles: If there is an occurrence of IRR or CRS Grade ≥ 3 in any of the subsequent cycles, permanently discontinue cevostamab regardless of recovery (see Grade 3 management guidelines). If there is an occurrence of a Grade ≤ 2 CRS in subsequent cycles, manage as indicated by severity (see Grade 1 or 2 management guidelines). Immediate actions: Stop further infusion of cevostamab. Provide supportive care and treat symptomatically as clinically indicated. ^c Monitor fluid balance; administer IV fluids bolus 250-500 mL up to 2000 mL total (avoid fluid overload); provide vasopressor support for hypotension with high and repeated doses if required. Hospitalize patient until complete resolution of signs and symptoms. Treat with IV corticosteroids (such as methylprednisolone 2 mg/kg/day or, if neurologic symptoms are present, dexamethasone 10 mg IV every 6 hours if needed). ^b Administer tocilizumab 8 mg/kg IV. ^d If there is no improvement after 8 hours, repeat tocilizumab administration. If no improvement within 8-12 hours after administering second dose of tocilizumab, manage as a Grade 4 event. Initiate workup and assess for signs and symptoms of MAS/HLH. Monitoring of cardiopulmonary and organ function in ICU is recommended. Provide oxygen for hypoxia. Restarting infusion: Do not restart infusion of cevostamab. Next cycle: If the patient had a Grade ≥ 2 IRR or CRS in any previous not cycle, permanently discontinue cevostamab. Patients who experience Grade 3 wheezing, bronchospasm, or generalized urticaria must be discontinued from cevostamab. If the patient recovers to Grade ≤ 1 for 3 consecutive days, cevostamab can be administered in next cycle as follows: Hospitalize patient for at least 24 hours after the mask infusion. Administer cevostamab at 50% of the initial infusion rate of the previous cycle if the event occurred during or within 24 hours of the infusion. ^e Pretreat with antihistamines, antipyretics, and/or analgesics Pretreat with IV corticosteroids (dexamethasone 20 mg (preferred) or methylprednisolone 80 mg). If the patient experienced Grade 3 CRS following the Cycle 1 Day 1 dose, the step-up dose must be repeated. Subsequent cycles: If a Grade ≥ 3 CRS recurs, permanently discontinue cevostamab. If there is an occurrence of a Grade ≤ 2 CRS in subsequent cycles, manage as indicated by severity (i.e., Grade 1 or 2 management guidelines). Stop cevostamab infusion. Follow all Grade 3 management guidelines. Patient requires ICU admission for hemodynamic monitoring, and/or mechanical ventilation, and/or IV fluids and vasopressors as needed.	
Grade 4	Fever ($\geq 38^\circ$ C. or 100.4° F. not attributable to any other cause) Hypotension: requires multiple vasopressors	

TABLE 3A-continued

Recommendations for management of cytokine release syndrome (CRS)	
Event ^{a, b}	Action to Be Taken ^b
Hypoxia: requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)	Administer tocilizumab 8 mg/kg IV (see footnote). ^d Treat with IV corticosteroids (such as methylprednisolone 2 mg/kg/day or, if neurologic symptoms are present, dexamethasone 10 mg IV every 6 hours if needed) For patients who are refractory to tocilizumab therapy, experimental therapies (e.g., siltuximab, anakinra, etapalumab, or LCK-inhibitors) ^b may be considered. Permanently discontinue study treatment.

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IV = intravenous; MAS = macrophage activation syndrome.

^a Refer to Table 2A for the complete description of grading of symptoms.

^b Guidance for CRS management based on Lee et al., *Biol Blood Marrow Transplant*, 25(4): 625-638, 2019 and Riegler et al. (2019).

^c Patients should be treated with acetaminophen and an antihistamine (e.g., diphenhydramine) if they have not been administered in the previous 4 hours. For bronchospasm, urticaria, or dyspnea, treat per institutional practice. Treat fever and neutropenia as required; consider broad-spectrum antibiotics and/or G-CSF if indicated.

^d Tocilizumab should be administered at dose of 8 mg/kg IV (8 mg/kg for patients ≥ 30 kg weight only; 12 mg/kg for patients < 30 kg weight; doses exceeding 800 mg per infusion are not recommended); repeat every 8 hours as necessary (up to a maximum of 4 doses).

^e If the patient does not experience CRS during the next infusion at the 50% reduced rate, the infusion rate can be increased to the initial rate in subsequent cycles. However, if this patient experiences another CRS event, the infusion rate should be reduced by 25%-50% depending on the severity of the event.

TABLE 3B

Recommendations for management of cevostamab infusion related reactions (IRR)	
Event ^a	Action to Be Taken
Grade 1-2	Slow infusion to $\leq 50\%$ or interrupt infusion. Give supportive treatment. ^b Upon symptom resolution, may resume infusion (if interrupted) at 50% starting rate. The infusion must remain at the lower rate, resulting in symptom resolution for the remainder of the infusion. ^c Premedicate with acetaminophen/paracetamol and an antihistamine such as diphenhydramine for all subsequent infusions. Notes: 1. For Grade 2 wheezing or urticaria, patient must be premedicated prior to subsequent doses. 2. If symptoms recur with the same or greater severity following the slower or interrupted infusion of cevostamab, the infusion must be stopped immediately. No further cevostamab should be administered for the cycle.
Grade 3	Discontinue cevostamab infusion. Do not re-initiate infusion for the current cycle. Give supportive treatment. ^b Admission to ICU is recommended to monitor cardiopulmonary and other organ functions. Provide oxygen for hypoxia and/or mechanical ventilation as needed. Subsequent cycles of cevostamab may be administered with premedication. Patients who experience Grade 3 wheezing, bronchospasm, or generalized urticaria at first occurrence must be discontinued from study treatment. Notes: 1. If symptoms recur despite premedications with the same or greater severity at subsequent cycles, the infusion must be stopped immediately and patient permanently discontinued from study treatment.
Grade 4	Discontinue infusion immediately. ^b Give supportive treatment. Admit to ICU to monitor cardiopulmonary and other organ functions. Provide oxygen for hypoxia and/or mechanical ventilation as needed. Permanently discontinue study treatment.

ICU = intensive care unit; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

^a Refer to NCI CTCAE v5.0 for the grading of symptoms.

^b Supportive treatment: Patients should be treated with acetaminophen/paracetamol and an antihistamine such as diphenhydramine if they have not been administered in the last 4 hours. Intravenous fluids (e.g., normal saline) may be administered as clinically indicated. For bronchospasm, urticaria, or dyspnea, antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators may be administered per institutional practice. Provide fluids and vasopressor support for hypotension if required.

^c Subsequent infusions of cevostamab may be started at the original rate.

ix. Management of Grade 2 CRS Events

[0352] If the subject has a grade 2 CRS event (e.g., a grade 2 CRS event in the absence of comorbidities or in the presence of minimal comorbidities) following administration of the therapeutic bispecific antibody, the method may further include treating the symptoms of the grade 2 CRS event while suspending treatment with the bispecific antibody. If the grade 2 CRS event then resolves to a grade≤1 CRS event for at least three consecutive days, the method may further include resuming treatment with the bispecific antibody without altering the dose. On the other hand, if the grade 2 CRS event does not resolve or worsens to a grade ≥3 CRS event within 24 hours of treating the symptoms of the grade 2 CRS event, the method may further involve administering to the subject an effective amount of an interleukin-6 receptor (IL-6R) antagonist (e.g., an anti-IL-6R antibody, e.g., tocilizumab (ACTEMRA®/ROACTEMRA®)) to manage the grade 2 or grade ≥3 CRS event. In some instances, tocilizumab is administered intravenously to the subject as a single dose of about 8 mg/kg. Other anti-IL-6R antibodies that could be used in combination with tocilizumab include sarilumab, vobarilizumab (ALX-0061), SA-237, and variants thereof.

[0353] If the subject has a grade 2 CRS event in the presence of extensive comorbidities following administration of the therapeutic bispecific antibody, the method may further include administering to the subject a first dose of an IL-6R antagonist (e.g., an anti-IL-6R antibody, e.g., tocilizumab (ACTEMRA®/ROACTEMRA®)) to manage the grade 2 CRS event while suspending treatment with the bispecific antibody. In some instances, the first dose of tocilizumab is administered intravenously to the subject at a dose of about 8 mg/kg. Other anti-IL-6R antibodies that could be used in combination with tocilizumab include sarilumab, vobarilizumab (ALX-0061), SA-237, and variants thereof. In some instances, if the grade 2 CRS event resolves to a grade≤1 CRS event within two weeks, the method further includes resuming treatment with the bispecific antibody at a reduced dose. In some instances, the reduced dose is 50% of the initial infusion rate of the previous cycle if the event occurred during or within 24 hours of the infusion. If, on the other hand, the grade 2 CRS event does not resolve or worsens to a grade ≥3 CRS event within 24 hours of treating the symptoms of the grade 2 CRS event, the method may further include administering to the subject one or more (e.g., one, two, three, four, or five or more) additional doses of an IL-6R antagonist (e.g., an anti-IL-6R antibody, e.g., tocilizumab) to manage the grade 2 or grade ≥3 CRS event. In some particular instances, the grade 2 CRS event does not resolve or worsens to a grade ≥3 CRS event within 24 hours of treating the symptoms of the grade 2 CRS event, and the method may further include administering to the subject one or more additional doses of tocilizumab to manage the grade 2 or grade ≥3 CRS event. In some instances, the one or more additional doses of tocilizumab is administered intravenously to the subject at a dose of about 1 mg/kg to about 15 mg/kg, e.g., about 4 mg/kg to about 10 mg/kg, e.g., about 6 mg/kg to about 10 mg/kg, e.g., about 8 mg/kg. In some instances, the method further includes administering to the subject an effective amount of a corticosteroid. The corticosteroid may be administered before, after, or concurrently with the one or more additional doses of tocilizumab or another anti-IL-6R antibody. In some instances, the corticosteroid is methylprednisolone. In some instances, the methylprednisolone is administered at a dose of about 1 mg/kg per day to about 5 mg/kg per day, e.g., about 2 mg/kg per day. In some instances, the corticosteroid is dexamethasone. In some instances, the dexamethasone is administered at a dose of about 10 mg (e.g., a single dose of about 10 mg intravenously) or at a dose of about 0.5 mg/kg/day.

x. Management of Grade 3 CRS Events

[0354] If the subject has a grade 3 CRS event following administration of the therapeutic bispecific antibody, the method may further include administering to the subject a first dose of an IL-6R antagonist (e.g., an anti-IL-6R antibody, e.g., tocilizumab (ACTEMRA®/ROACTEMRA®)) to manage the grade 3 CRS event while suspending treatment with the bispecific antibody. In some instances, the first dose of tocilizumab is administered intravenously to the subject at a dose of about 8 mg/kg. Other anti-IL-6R antibodies that could be used in combination with tocilizumab include sarilumab, vobarilizumab (ALX-0061), SA-237, and variants thereof. In some instances, the subject recovers (e.g., is afebrile and off vasopressors) within 8 hours following treatment with the bispecific antibody, and the method further includes resuming treatment with the bispecific antibody at a reduced dose. In some instances, the reduced dose is 50% of the initial infusion rate of the previous cycle if the event occurred during or within 24 hours of the infusion. In other instances, if the grade 3 CRS event does not resolve or worsens to a grade 4 CRS event within 24 hours of treating the symptoms of the grade 3 CRS event, the method may further include administering to the subject one or more (e.g., one, two, three, four, or five or more) additional doses of an IL-6R antagonist (e.g., an anti-IL-6R antibody, e.g., tocilizumab) to manage the grade 3 or grade 4 CRS event. In some particular instances, the grade 3 CRS event does not resolve or worsens to a grade 4 CRS event within 24 hours of treating the symptoms of the grade 3 CRS event, and the method further includes administering to the subject one or more additional doses of tocilizumab to manage the grade 3 or grade 4 CRS event. In some instances, the one or more additional doses of tocilizumab is administered intravenously to the subject at a dose of about 1 mg/kg to about 15 mg/kg, e.g., about 4 mg/kg to about 10 mg/kg, e.g., about 6 mg/kg to about 10 mg/kg, e.g., about 8 mg/kg. In some instances, the method further includes administering to the subject an effective amount of a corticosteroid. The corticosteroid may be administered before, after, or concurrently with the one or more additional doses of tocilizumab or another anti-IL-6R antibody. In some instances, the corticosteroid is administered intravenously to the subject. In some instances, the corticosteroid is methylprednisolone. In some instances, the methylprednisolone is administered at a dose of about 1 mg/kg per day to about 5 mg/kg per day, e.g., about 2 mg/kg per day. In some instances, the corticosteroid is dexamethasone. In some instances, the dexamethasone is administered at a dose of about 10 mg (e.g., a single dose of about 10 mg intravenously) or at a dose of about 0.5 mg/kg/day.

xi Management of Grade 4 CRS Events

[0355] If the subject has a grade 4 CRS event following administration of the therapeutic bispecific antibody, the method may further include administering to the subject a first dose of an IL-6R antagonist (e.g., an anti-IL-6R anti-

body, e.g., tocilizumab (ACTEMRA®/ROACTEMRA®)) to manage the grade 4 CRS event and permanently discontinuing treatment with the bispecific antibody. In some instances, the first dose of tocilizumab is administered intravenously to the subject at a dose of about 8 mg/kg. Other anti-IL-6R antibodies that could be used in combination with tocilizumab include sarilumab, vobalizumab (ALX-0061), SA-237, and variants thereof. The grade 4 CRS event may, in some instances, resolve within 24 of treating the symptoms of the grade 4 CRS event. If the grade 4 CRS event does not resolve within 24 hours of treating the symptoms of the grade 4 CRS event, the method may further include administering to the subject one or more additional doses of an IL-6R antagonist (e.g., an anti-IL-6R antibody, e.g., tocilizumab (ACTEMRA®/ROACTEMRA®)) to manage the grade 4 CRS event. In some particular instances, the grade 4 CRS event does not resolve within 24 hours of treating the symptoms of the grade 4 CRS event, and the method further includes administering to the subject one or more (e.g., one, two, three, four, or five or more) additional doses of tocilizumab to manage the grade 4 CRS event. In some instances, the one or more additional doses of tocilizumab is administered intravenously to the subject at a dose of about 1 mg/kg to about 15 mg/kg, e.g., about 4 mg/kg to about 10 mg/kg, e.g., about 6 mg/kg to about 10 mg/kg, e.g., about 8 mg/kg. In some instances, the method further includes administering to the subject an effective amount of a corticosteroid. The corticosteroid may be administered before, after, or concurrently with the one or more additional doses of tocilizumab or another anti-IL-6R antibody. In some instances, the corticosteroid is administered intravenously to the subject. In some instances, the corticosteroid is methylprednisolone. In some instances, the methylprednisolone is administered at a dose of about 1 mg/kg per day to about 5 mg/kg per day, e.g., about 2 mg/kg per day. In some instances, the corticosteroid is dexamethasone. In some instances, the dexamethasone is administered at a dose of about 10 mg (e.g., a single dose of about 10 mg intravenously) or at a dose of about 0.5 mg/kg/day.

xii. Acetaminophen or Paracetamol

[0356] In another instance, the additional therapeutic agent is an effective amount of acetaminophen or paracetamol. The acetaminophen or paracetamol may be administered orally to the subject, e.g., administered orally at a dose of between about 500 mg to about 1000 mg. In some aspects, the acetaminophen or paracetamol is administered to the subject as a premedication, e.g., is administered prior to the administration of the bispecific anti-FcRH5/anti-CD3 antibody.

xiii. Diphenhydramine

[0357] In another instance, the additional therapeutic agent is an effective amount of diphenhydramine. The diphenhydramine may be administered orally to the subject, e.g., administered orally at a dose of between about 25 mg to about 50 mg. In some aspects, the diphenhydramine is administered to the subject as a premedication, e.g., is administered prior to the administration of the bispecific anti-FcRH5/anti-CD3 antibody.

xiv. Anti-Myeloma Agents

[0358] In another instance, the additional therapeutic agent is an effective amount of an anti-myeloma agent, e.g., an anti-myeloma agent that augments and/or complements T-cell-mediated killing of myeloma cells. The anti-myeloma agent may be, e.g., pomalidomide, daratumumab, and/or a

B-cell maturation antigen (BCMA)-directed therapy (e.g., an antibody-drug conjugate targeting BCMA (BCMA-ADC)). In some aspects, the anti-myeloma agent is administered in four-week cycles.

xv. Other Combination Therapies

[0359] In some aspects, the one or more additional therapeutic agents comprise a PD-1 axis binding antagonist, an immunomodulatory agent, an anti-neoplastic agent, a chemotherapeutic agent, a growth inhibitory agent, an anti-angiogenic agent, a radiation therapy, a cytotoxic agent, a cell-based therapy, or a combination thereof.

xvi. PD-1 Axis Binding Antagonists

[0360] In some aspects, the one or more additional therapeutic agents comprise a PD-1 axis binding antagonist. PD-1 axis binding antagonists may include PD-L1 binding antagonists, PD-1 binding antagonists, and PD-L2 binding antagonists. Any suitable PD-1 axis binding antagonist may be used.

[0361] In some instances, the PD-L1 binding antagonist inhibits the binding of PD-L1 to one or more of its ligand binding partners. In other instances, the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1. In yet other instances, the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1. In some instances, the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1. The PD-L1 binding antagonist may be, without limitation, an antibody, an antigen-binding fragment thereof, an immunoadhesin, a fusion protein, an oligopeptide, or a small molecule. In some instances, the PD-L1 binding antagonist is a small molecule that inhibits PD-L1 (e.g., GS-4224, INCB086550, MAX-10181, INCB090244, CA-170, or ABSK041). In some instances, the PD-L1 binding antagonist is a small molecule that inhibits PD-L1 and VISTA. In some instances, the PD-L1 binding antagonist is CA-170 (also known as AUPM-170). In some instances, the PD-L1 binding antagonist is a small molecule that inhibits PD-L1 and TIM3. In some instances, the small molecule is a compound described in WO 2015/033301 and/or WO 2015/033299.

[0362] In some instances, the PD-L1 binding antagonist is an anti-PD-L1 antibody. A variety of anti-PD-L1 antibodies are contemplated and described herein. In any of the instances herein, the isolated anti-PD-L1 antibody can bind to a human PD-L1, for example a human PD-L1 as shown in UniProtKB/Swiss-Prot Accession No. Q9NZQ7-1, or a variant thereof. In some instances, the anti-PD-L1 antibody is capable of inhibiting binding between PD-L1 and PD-1 and/or between PD-L1 and B7-1. In some instances, the anti-PD-L1 antibody is a monoclonal antibody. In some instances, the anti-PD-L1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments. In some instances, the anti-PD-L1 antibody is a humanized antibody. In some instances, the anti-PD-L1 antibody is a human antibody. Exemplary anti-PD-L1 antibodies include atezolizumab, MDX-1105, MEDI4736 (durvalumab), MSB0010718C (avelumab), SHR-1316, CS1001, enavafolimab, TQB2450, ZKAB001, LP-002, CX-072, IMC-001, KL-A167, APL-502, cosibelimab, lodapolimab, FAZ053, TG-1501, BGB-A333, BCD-135, AK-106, LDP, GR1405, HLX20, MSB2311, RC98, PDL-GEX, KD036, KY1003, YBL-007, and HS-636. In some instances, the anti-PD-L1 antibody is atezolizumab. Examples of anti-PD-L1 antibodies useful in the methods of this invention and methods of making them are described in

International Patent Application Publication No. WO 2010/077634 and U.S. Pat. No. 8,217,149, each of which is incorporated herein by reference in its entirety.

[0363] In some instances, the anti-PD-L1 antibody is avelumab (CAS Registry Number: 1537032-82-8). Avelumab, also known as MSB0010718C, is a human monoclonal IgG1 anti-PD-L1 antibody (Merck KGaA, Pfizer).

[0364] In some instances, the anti-PD-L1 antibody is durvalumab (CAS Registry Number: 1428935-60-7). Durvalumab, also known as MEDI4736, is an Fc-optimized human monoclonal IgG1 kappa anti-PD-L1 antibody (MedImmune, AstraZeneca) described in WO 2011/066389 and US 2013/034559.

[0365] In some instances, the anti-PD-L1 antibody is MDX-1105 (Bristol Myers Squibb). MDX-1105, also known as BMS-936559, is an anti-PD-L1 antibody described in WO 2007/005874.

[0366] In some instances, the anti-PD-L1 antibody is LY3300054 (Eli Lilly).

[0367] In some instances, the anti-PD-L1 antibody is STI-A1014 (Sorrento). STI-A1014 is a human anti-PD-L1 antibody.

[0368] In some instances, the anti-PD-L1 antibody is KN035 (Suzhou Alphamab). KN035 is single-domain antibody (dAB) generated from a camel phage display library.

[0369] In some instances, the anti-PD-L1 antibody comprises a cleavable moiety or linker that, when cleaved (e.g., by a protease in the tumor microenvironment), activates an antibody antigen binding domain to allow it to bind its antigen, e.g., by removing a non-binding steric moiety. In some instances, the anti-PD-L1 antibody is CX-072 (CytomX Therapeutics).

[0370] In some instances, the anti-PD-L1 antibody comprises the six HVR sequences (e.g., the three heavy chain HVRs and the three light chain HVRs) and/or the heavy chain variable domain and light chain variable domain from an anti-PD-L1 antibody described in US20160108123, WO 2016/000619, WO 2012/145493, U.S. Pat. No. 9,205,148, WO 2013/181634, or WO 2016/061142.

[0371] In some instances, the PD-1 axis binding antagonist is a PD-1 binding antagonist. For example, in some instances, the PD-1 binding antagonist inhibits the binding of PD-1 to one or more of its ligand binding partners. In some instances, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1. In other instances, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2. In yet other instances, the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2. The PD-1 binding antagonist may be, without limitation, an antibody, an antigen-binding fragment thereof, an immunoadhesin, a fusion protein, an oligopeptide, or a small molecule. In some instances, the PD-1 binding antagonist is an immunoadhesin (e.g., an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region (e.g., an Fc region of an immunoglobulin sequence). For example, in some instances, the PD-1 binding antagonist is an Fc-fusion protein. In some instances, the PD-1 binding antagonist is AMP-224. AMP-224, also known as B7-DC Ig, is a PD-L2-Fc fusion soluble receptor described in WO 2010/027827 and WO 2011/066342. In some instances, the PD-1 binding antagonist is a peptide or small molecule compound. In some instances, the PD-1 binding antagonist is AUNP-12 (PierreFabre/Aurigene). See, e.g., WO 2012/168944, WO 2015/036927, WO 2015/044900, WO 2015/

033303, WO 2013/144704, WO 2013/132317, and WO 2011/161699. In some instances, the PD-1 binding antagonist is a small molecule that inhibits PD-1.

[0372] In some instances, the PD-1 binding antagonist is an anti-PD-1 antibody. A variety of anti-PD-1 antibodies can be utilized in the methods and uses disclosed herein. In any of the instances herein, the PD-1 antibody can bind to a human PD-1 or a variant thereof. In some instances, the anti-PD-1 antibody is a monoclonal antibody. In some instances, the anti-PD-1 antibody is an antibody fragment selected from the group consisting of Fab, Fab', Fab'-SH, Fv, scFv, and (Fab')₂ fragments. In some instances, the anti-PD-1 antibody is a humanized antibody. In other instances, the anti-PD-1 antibody is a human antibody. Exemplary anti-PD-1 antagonist antibodies include nivolumab, pembrolizumab, MEDI-0680, PDR001 (spartalizumab), REGN2810 (cemiplimab), BGB-108, prolgolimab, camrelizumab, sintilimab, tislelizumab, toripalimab, dostarlimab, retifanlimab, sasanlimab, penpulimab, CS1003, HLX10, SCT-110A, zimberelimab, balstilimab, genolizumab, BI 754091, cetrelimab, YBL-006, BAT1306, HX008, budigalimab, AMG 404, CX-188, JTX-4014, 609A, Sym021, LZM009, F520, SG001, AM0001, ENUM 244C8, ENUM 388D4, STI-1110, AK-103, and hAb21.

[0373] In some instances, the anti-PD-1 antibody is nivolumab (CAS Registry Number: 946414-94-4). Nivolumab (Bristol-Myers Squibb/Ono), also known as MDX-1106-04, MDX-1106, ONO-4538, BMS-936558, and OPDIVO®, is an anti-PD-1 antibody described in WO 2006/121168.

[0374] In some instances, the anti-PD-1 antibody is pembrolizumab (CAS Registry Number: 1374853-91-4). Pembrolizumab (Merck), also known as MK-3475, Merck 3475, lambrolizumab, SCH-900475, and KEYTRUDA®, is an anti-PD-1 antibody described in WO 2009/114335.

[0375] In some instances, the anti-PD-1 antibody is MEDI-0680 (AMP-514; AstraZeneca). MEDI-0680 is a humanized IgG4 anti-PD-1 antibody.

[0376] In some instances, the anti-PD-1 antibody is PDR001 (CAS Registry No. 1859072-53-9; Novartis). PDR001 is a humanized IgG4 anti-PD-1 antibody that blocks the binding of PD-L1 and PD-L2 to PD-1.

[0377] In some instances, the anti-PD-1 antibody is REGN2810 (Regeneron). REGN2810 is a human anti-PD-1 antibody.

[0378] In some instances, the anti-PD-1 antibody is BGB-108 (BeiGene).

[0379] In some instances, the anti-PD-1 antibody is BGB-A317 (BeiGene).

[0380] In some instances, the anti-PD-1 antibody is JS-001 (Shanghai Junshi). JS-001 is a humanized anti-PD-1 antibody.

[0381] In some instances, the anti-PD-1 antibody is STI-A1110 (Sorrento). STI-A1110 is a human anti-PD-1 antibody.

[0382] In some instances, the anti-PD-1 antibody is INCNSHR-1210 (Incyte). INCNSHR-1210 is a human IgG4 anti-PD-1 antibody.

[0383] In some instances, the anti-PD-1 antibody is PF-06801591 (Pfizer).

[0384] In some instances, the anti-PD-1 antibody is TSR-042 (also known as ANB011; Tesaro/AnaptysBio).

[0385] In some instances, the anti-PD-1 antibody is AM0001 (ARMO Biosciences).

[0386] In some instances, the anti-PD-1 antibody is ENUM 244C8 (Enumeral Biomedical Holdings). ENUM 244C8 is an anti-PD-1 antibody that inhibits PD-1 function without blocking binding of PD-L1 to PD-1.

[0387] In some instances, the anti-PD-1 antibody is ENUM 388D4 (Enumeral Biomedical Holdings). ENUM 388D4 is an anti-PD-1 antibody that competitively inhibits binding of PD-L1 to PD-1.

[0388] In some instances, the anti-PD-1 antibody comprises the six HVR sequences (e.g., the three heavy chain HVRs and the three light chain HVRs) and/or the heavy chain variable domain and light chain variable domain from an anti-PD-1 antibody described in WO 2015/112800, WO 2015/112805, WO 2015/112900, US 20150210769, WO2016/089873, WO 2015/035606, WO 2015/085847, WO 2014/206107, WO 2012/145493, U.S. Pat. No. 9,205,148, WO 2015/119930, WO 2015/119923, WO 2016/032927, WO 2014/179664, WO 2016/106160, and WO 2014/194302.

[0389] In some instances, the PD-1 axis binding antagonist is a PD-L2 binding antagonist. In some instances, the PD-L2 binding antagonist is a molecule that inhibits the binding of PD-L2 to its ligand binding partners. In a specific aspect, the PD-L2 binding ligand partner is PD-1. The PD-L2 binding antagonist may be, without limitation, an antibody, an antigen-binding fragment thereof, an immunoadhesin, a fusion protein, an oligopeptide, or a small molecule.

[0390] In some instances, the PD-L2 binding antagonist is an anti-PD-L2 antibody. In any of the instances herein, the anti-PD-L2 antibody can bind to a human PD-L2 or a variant thereof. In some instances, the anti-PD-L2 antibody is a monoclonal antibody. In some instances, the anti-PD-L2 antibody is an antibody fragment selected from the group consisting of Fab, Fab', Fab'-SH, Fv, scFv, and (Fab')₂ fragments. In some instances, the anti-PD-L2 antibody is a humanized antibody. In other instances, the anti-PD-L2 antibody is a human antibody. In a still further specific aspect, the anti-PD-L2 antibody has reduced or minimal effector function. In a still further specific aspect, the minimal effector function results from an "effector-less Fc mutation" or aglycosylation mutation. In still a further instance, the effector-less Fc mutation is an N297A or D265A/N297A substitution in the constant region. In some instances, the isolated anti-PD-L2 antibody is aglycosylated.

xvii. Growth Inhibitory Agents

[0391] In some aspects, the one or more additional therapeutic agents comprise a growth inhibitory agent. Exemplary growth inhibitory agents include agents that block cell cycle progression at a place other than S phase, e.g., agents that induce G1 arrest (e.g., DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, or ara-C) or M-phase arrest (e.g., vincristine, vinblastine, taxanes (e.g., paclitaxel and docetaxel), doxorubicin, epirubicin, daunorubicin, etoposide, or bleomycin).

xviii. Radiation Therapies

[0392] In some aspects, the one or more additional therapeutic agents comprise a radiation therapy. Radiation therapies include the use of directed gamma rays or beta rays to induce sufficient damage to a cell so as to limit its ability to function normally or to destroy the cell altogether. Typical treatments are given as a one-time administration and typical dosages range from 10 to 200 units (Grays) per day.

xix. Cytotoxic Agents

[0393] In some aspects, the additional therapeutic agent is a cytotoxic agent, e.g., a substance that inhibits or prevents a cellular function and/or causes cell death or destruction. Cytotoxic agents include, but are not limited to, radioactive isotopes (e.g., At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², Pb²¹², and radioactive isotopes of Lu); chemotherapeutic agents or drugs (e.g., methotrexate, *vinca* alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents); growth inhibitory agents; enzymes and fragments thereof such as nucleolytic enzymes; antibiotics; toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof; and antitumor or anticancer agents.

xx. Additional Anti-Cancer Therapies

[0394] In some instances, the methods further involve administering to the patient an effective amount of an additional therapeutic agent. In some instances, the additional therapeutic agent is selected from the group consisting of an anti-neoplastic agent, a chemotherapeutic agent, a growth inhibitory agent, an anti-angiogenic agent, a radiation therapy, a cytotoxic agent, and combinations thereof. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a chemotherapy or chemotherapeutic agent. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a radiation therapy agent. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a targeted therapy or targeted therapeutic agent. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an immunotherapy or immunotherapeutic agent, for example a monoclonal antibody. In some instances, the additional therapeutic agent is an agonist directed against a co-stimulatory molecule. In some instances, the additional therapeutic agent is an antagonist directed against a co-inhibitory molecule.

[0395] Without wishing to be bound to theory, it is thought that enhancing T-cell stimulation, by promoting a co-stimulatory molecule or by inhibiting a co-inhibitory molecule, may promote tumor cell death thereby treating or delaying progression of cancer. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody may be administered in conjunction with an agonist directed against a co-stimulatory molecule. In some instances, a co-stimulatory molecule may include CD40, CD226, CD28, OX40, GITR, CD137, CD27, HVEM, or CD127. In some instances, the agonist directed against a co-stimulatory molecule is an agonist antibody that binds to CD40, CD226, CD28, OX40, GITR, CD137, CD27, HVEM, or CD127. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody may be administered in conjunction with an antagonist directed against a co-inhibitory molecule. In some instances, a co-inhibitory molecule may include CTLA-4 (also known as CD152), TIM-3, BTLA, VISTA, LAG-3, B7-H3, B7-H4, IDO, TIGIT, MICA/B, or arginase. In some instances, the antagonist directed against a co-inhibitory molecule is an antagonist antibody that binds to CTLA-4, TIM-3, BTLA, VISTA, LAG-3, B7-H3, B7-H4, IDO, TIGIT, MICA/B, or arginase.

[0396] In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in

conjunction with an antagonist directed against CTLA-4 (also known as CD152), e.g., a blocking antibody. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with ipilimumab (also known as MDX-010, MDX-101, or YERVOY®). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody may be administered in conjunction with tremelimumab (also known as ticilimumab or CP-675,206). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an antagonist directed against B7-H3 (also known as CD276), e.g., a blocking antibody. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with MGA271. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an antagonist directed against a TGF-beta, e.g., metelimumab (also known as CAT-192), fresolimumab (also known as GC1008), or LY2157299.

[0397] In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a treatment comprising adoptive transfer of a T-cell (e.g., a cytotoxic T-cell or CTL) expressing a chimeric antigen receptor (CAR). In some instances, bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a treatment comprising adoptive transfer of a T-cell comprising a dominant-negative TGF beta receptor, e.g., a dominant-negative TGF beta type II receptor. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a treatment comprising a HERCREEM protocol (see, e.g., ClinicalTrials.gov Identifier NCT00889954).

[0398] In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an agonist directed against CD137 (also known as TNFRSF9, 4-1BB, or ILA), e.g., an activating antibody. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with urelumab (also known as BMS-663513). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an agonist directed against CD40, e.g., an activating antibody. In some instances, bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with CP-870893. In some instances, bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an agonist directed against OX40 (also known as CD134), e.g., an activating antibody. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an anti-OX40 antibody (e.g., AgonOX). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an agonist directed against CD27, e.g., an activating antibody. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with CDX-1127. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an antagonist directed against indoleamine-2,3-dioxygenase (IDO). In some instances, with the IDO antagonist is 1-methyl-D-tryptophan (also known as 1-D-MT).

[0399] In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an antibody-drug conjugate. In some instances, the antibody-drug conjugate comprises mertansine or monomethyl auristatin E (MMAE). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an anti-NaPi2b antibody-MMAE conjugate (also known as DNIB0600A or RG7599). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with trastuzumab emtansine (also known as T-DM1, ado-trastuzumab emtansine, or KADCYLA®, Genentech). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with DMUC5754A. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an antibody-drug conjugate targeting the endothelin B receptor (EDNBR), e.g., an antibody directed against EDNBR conjugated with MMAE.

[0400] In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an anti-angiogenesis agent. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an antibody directed against a VEGF, e.g., VEGF-A. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with bevacizumab (also known as AVASTIN®, Genentech). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an antibody directed against angiopoietin 2 (also known as Ang2). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with MEDI3617.

[0401] In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an antineoplastic agent. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an agent targeting CSF-1R (also known as M-CSFR or CD115). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with anti-CSF-1R (also known as IMC-CS4). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an interferon, for example interferon alpha or interferon gamma. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with Roferon-A (also known as recombinant Interferon alpha-2a). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with GM-CSF (also known as recombinant human granulocyte macrophage colony stimulating factor, rhu GM-CSF, sargramostim, or LEUKINE®). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with IL-2 (also known as aldesleukin or PROLEUKIN®). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with IL-12. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an antibody targeting CD20. In some instances, the antibody targeting CD20 is obinutuzumab (also known as GA101 or

GAZYVAR) or rituximab. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an antibody targeting GITR. In some instances, the antibody targeting GITR is TRX518.

[0402] In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a cancer vaccine. In some instances, the cancer vaccine is a peptide cancer vaccine, which in some instances is a personalized peptide vaccine. In some instances, the peptide cancer vaccine is a multivalent long peptide, a multi-peptide, a peptide cocktail, a hybrid peptide, or a peptide-pulsed dendritic cell vaccine (see, e.g., Yamada et al., *Cancer Sci.* 104:14-21, 2013). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an adjuvant. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a treatment comprising a TLR agonist, e.g., Poly-ICLC (also known as HILTONOL®), LPS, MPL, or CpG ODN. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with tumor necrosis factor (TNF) alpha. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with IL-1. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with HMGB1. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an IL-10 antagonist. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an IL-4 antagonist. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an IL-13 antagonist. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an HVEM antagonist. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an ICOS agonist, e.g., by administration of ICOS-L, or an agonistic antibody directed against ICOS. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a treatment targeting CX3CL1. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a treatment targeting CXCL9. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a treatment targeting CXCL10. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a treatment targeting CCL5. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an LFA-1 or ICAM1 agonist. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a Selectin agonist.

[0403] In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a targeted therapy. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an inhibitor of B-Raf. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with vemurafenib (also known as ZELBORA®). In

some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with dabrafenib (also known as TAFINLAR®). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with erlotinib (also known as TARCEVA®). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an inhibitor of a MEK, such as MEK1 (also known as MAP2K1) or MEK2 (also known as MAP2K2). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with cobimetinib (also known as GDC-0973 or XL-518). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with trametinib (also known as MEKINIST®). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an inhibitor of K-Ras. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an inhibitor of c-Met. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with omartuzumab (also known as MetMAB). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an inhibitor of Alk. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with AF802 (also known as CH5424802 or alemtuzumab). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an inhibitor of a phosphatidylinositol 3-kinase (PI3K). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with BKM120. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with idelalisib (also known as GS-1101 or CAL-101). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with perifosine (also known as KRX-0401). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an inhibitor of an Akt. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with MK2206. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody may be administered in conjunction with GSK690693. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with GDC-0941. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with an inhibitor of mTOR. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with sirolimus (also known as rapamycin). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with temsirolimus (also known as CCI-779 or TORISEL®). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with everolimus (also known as RAD001). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with ridaforolimus (also known as AP-23573, MK-8669, or deforolimus). In some instances, a bispecific anti-FcRH5/

anti-CD3 antibody and lenalidomide may be administered in conjunction with OSI-027. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with AZD8055. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with INK128. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a dual PI3K/mTOR inhibitor. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with XL765. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with GDC-0980. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with BEZ235 (also known as NVP-BEZ235). In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with BGT226. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with GSK2126458. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with PF-04691502. In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with PF-05212384 (also known as PKI-587).

[0404] In some instances, a bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide may be administered in conjunction with a chemotherapeutic agent. A chemotherapeutic agent is a chemical compound useful in the treatment of cancer. Exemplary chemotherapeutic agents include, but are not limited to erlotinib (TARCEVA®, Genentech/OSI Pharm.), anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), antibodies such as alemtuzumab (Campath), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), pertuzumab (OMNITARG®, 2C4, Genentech), or trastuzumab (HERCEPTIN®, Genentech), EGFR inhibitors (EGFR antagonists), tyrosine kinase inhibitors, and chemotherapeutic agents also include non-steroidal anti-inflammatory drugs (NSAIDs) with analgesic, anti-pyretic and anti-inflammatory effects.

[0405] In instances for which the methods described herein involve a combination therapy, such as a particular combination therapy noted above, the combination therapy encompasses the co-administration of the bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide with one or more additional therapeutic agents, and such co-administration may be combined administration (where two or more therapeutic agents are included in the same or separate formulations) or separate administration, in which case, administration of the bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent or agents. In one embodiment, administration of the bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide and administration of an additional therapeutic agent or exposure to radiotherapy can occur within about one month, or within about one, two or three weeks, or within about one, two, three, four, five, or six days, of each other.

[0406] In some aspects, the subject does not have an increased risk of CRS (e.g., has not experienced Grade 3+

CRS during treatment with a bispecific antibody or CAR-T therapy; does not have detectable circulating plasma cells; and/or does not have extensive extramedullary disease).

C. Cancers

[0407] Any of the methods of the invention described herein may be useful for treating a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM (e.g., an MM with a high-risk cytogenetic feature))). In some aspects, the subject's cancer has one or more high-risk cytogenetic features. In some examples, the high-risk cytogenetic feature comprises one or more of the following: translocation events t(4;14) or t(14;16), del(17p), or 1q gain.

[0408] Other examples of B cell proliferative disorders/malignancies amenable to treatment with a bispecific anti-FcRH5/anti-CD3 antibody in accordance with the methods described herein include, without limitation, non-Hodgkin's lymphoma (NHL), including diffuse large B cell lymphoma (DLBCL), which may be relapsed or refractory DLBCL, as well as other cancers including germinal-center B cell-like (GCB) diffuse large B cell lymphoma (DLBCL), activated B cell-like (ABC) DLBCL, follicular lymphoma (FL), mantle cell lymphoma (MCL), acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL), marginal zone lymphoma (MZL), small lymphocytic leukemia (SLL), lymphoplasmacytic lymphoma (LL), Waldenstrom macroglobulinemia (WM), central nervous system lymphoma (CNSL), Burkitt's lymphoma (BL), B cell prolymphocytic leukemia, splenic marginal zone lymphoma, hairy cell leukemia, splenic lymphoma/leukemia, unclassifiable, splenic diffuse red pulp small B cell lymphoma, hairy cell leukemia variant, Waldenstrom macroglobulinemia, heavy chain diseases, α heavy chain disease, γ heavy chain disease, μ heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone, extraosseous plasmacytoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), nodal marginal zone lymphoma, pediatric nodal marginal zone lymphoma, pediatric follicular lymphoma, primary cutaneous follicle centre lymphoma, T cell/histiocyte rich large B cell lymphoma, primary DLBCL of the CNS, primary cutaneous DLBCL, leg type, EBV-positive DLBCL of the elderly, DLBCL associated with chronic inflammation, lymphomatoid granulomatosis, primary mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, ALK-positive large B cell lymphoma, plasmablastic lymphoma, large B cell lymphoma arising in HHV8-associated multicentric Castleman disease, primary effusion lymphoma: B cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma, and B cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin's lymphoma. Further examples of B cell proliferative disorders include, but are not limited to, multiple myeloma (MM); low grade/follicular NHL; small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; AIDS-related lymphoma; and acute lymphoblastic leukemia (ALL); chronic myeloblastic leukemia; and post-transplant lymphoproliferative disorder (PTLD). Further examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies, including B cell lymphomas. More particular examples of such cancers include,

but are not limited to, low grade/follicular NHL; small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; AIDS-related lymphoma; and acute lymphoblastic leukemia (ALL); chronic myeloblastic leukemia; and post-transplant lymphoproliferative disorder (PTLD). Solid tumors that may be amenable to treatment with a bispecific anti- FcRH5 /anti-CD3 antibody in accordance with the methods described herein include squamous cell cancer (e.g., epithelial squamous cell cancer), lung cancer including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer and gastrointestinal stromal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, cancer of the urinary tract, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, melanoma, superficial spreading melanoma, lentigo maligna melanoma, acral lentiginous melanomas, nodular melanomas, as well as abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), Meigs' syndrome, brain, as well as head and neck cancer, and associated metastases. In certain embodiments, cancers that are amenable to treatment by the antibodies disclosed herein include breast cancer, colorectal cancer, rectal cancer, non-small cell lung cancer, glioblastoma, non-Hodgkins lymphoma (NHL), renal cell cancer, prostate cancer, liver cancer, pancreatic cancer, soft-tissue sarcoma, Kaposi's sarcoma, carcinoid carcinoma, head and neck cancer, ovarian cancer, and mesothelioma.

D. Prior Anti-Cancer Therapy

[0409] In some aspects, the subject has previously been treated for a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM (e.g., an MM with a high-risk cytogenetic feature)))).

[0410] In some aspects, the subject has received an induction therapy. Any suitable induction therapy may be used. Exemplary induction therapies for MM include, but are not limited to, CyBorD regimen (cyclophosphamide, bortezomib and dexamethasone); VRD regimen (bortezomib, lenalidomide and dexamethasone); VRD lite (reduced dose and schedule of bortezomib, lenalidomide, and dexamethasone); thalidomide and dexamethasone; lenalidomide and low-dose dexamethasone; bortezomib and dexamethasone; Vd regimen (bortezomib and dexamethasone); VTD regimen (bortezomib, thalidomide and dexamethasone); bortezomib, cyclophosphamide and prednisone; bortezomib, doxorubicin and dexamethasone; DARZALEX FASPRO® (daratumumab and hyaluronidase), bortezomib, ALK-ERAN® (melphalan) and prednisone; DARZALEX FASPRO® (daratumumab and hyaluronidase), lenalidomide and dexamethasone; DARZALEX FASPRO® (daratumumab and hyaluronidase), bortezomib, thalidomide, and dexamethasone; and liposomal doxorubicin, vincristine, and dexamethasone.

[0411] In some aspects, the subject has undergone autologous stem cell transplantation (ASCT). For example, in

some aspects, the subject has undergone ASCT within about 100 days (e.g., within 100 days, within 90 days, within 80 days, within 70 days, within 60 days, within 50 days, within 40 days, within 30 days, within 20 days, within 10 days, within 5 days, or within 1 day of the onset of the method (e.g., the first administration of the bispecific antibody and/or the lenalidomide). In some examples, the subject has an absence of progressive disease.

[0412] In some examples, the bispecific antibody and lenalidomide are administered to the patient as a post-transplant maintenance therapy.

[0413] In some aspects, the subject has received at least one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, or more than fifteen lines of treatment for the B cell proliferative disorder, e.g., is 2L+, 3L+, 4L+, 5L+, 6L+, 7L+, 8L+, 9L+, 10L+, 11L+, 12L+, 13L+, 14L+, or 15L+.

[0414] In some aspects, the subject has received at least three prior lines of treatment for the cancer (e.g., the hematologic cancer (e.g., the B cell proliferative disorder (e.g., the MM (e.g., the MM with a high-risk cytogenetic feature))))). e.g., is 4L+, e.g., has received three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, or more than fifteen lines of treatment. In some aspects, the subject has relapsed or refractory (R/R) multiple myeloma (MM), e.g., has 4L+R/R MM.

[0415] In some aspects, the prior lines of treatment include one or more of a proteasome inhibitor (PI), e.g., bortezomib, carfilzomib, or ixazomib; an immunomodulatory drug (IMiD), e.g., thalidomide, lenalidomide, or pomalidomide; an autologous stem cell transplant (ASCT); an anti-CD38 agent, e.g., daratumumab (DARZALEX®) (U.S. Pat. No. 7,829,673 and U.S. Pub. No: 20160067205 A1), "MOR202" (U.S. Pat. No. 8,263,746), isatuximab (SAR-650984); a CAR-T therapy; a therapy comprising a bispecific antibody; an anti-SLAMF7 therapeutic agent (e.g., an anti-SLAMF7 antibody, e.g., elotuzumab); a nuclear export inhibitor (e.g., selinexor); and a histone deacetylase (HDAC) inhibitor (e.g., panobinostat). In some aspects, the prior lines of treatment include an antibody-drug conjugate (ADC). In some aspects, the prior lines of treatment include a B-cell maturation antigen (BCMA)-directed therapy, e.g., an antibody-drug conjugate targeting BCMA (BCMA-ADC).

[0416] In some aspects, the prior lines of treatment include all three of a proteasome inhibitor (PI), an IMiD, and an anti-CD38 agent (e.g., daratumumab).

[0417] In some aspects, the cancer (e.g., the hematologic cancer (e.g., the B cell proliferative disorder (e.g., the MM (e.g., the MM with a high-risk cytogenetic feature)))) is refractory to the lines of treatment, e.g., is refractory to one or more of daratumumab, a PI, an IMiD, an ASCT, an anti-CD38 agent, a CAR-T therapy, a therapy comprising a bispecific antibody, an anti-SLAMF7 therapeutic agent, a nuclear export inhibitor, a HDAC inhibitor, an ADC, or a BCMA-directed therapy. In some aspects, the B cell proliferative disorder (e.g., MM) is refractory to daratumumab.

E. Risk-Benefit Profile

[0418] The methods described herein may result in an improved benefit-risk profile for patients having a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM (e.g., an MM with a high-risk cytogenetic feature))))). In some instances, treatment using the methods described herein that result in administering the

bispecific anti-FcRH5/anti-CD3 antibody and lenalidomide in the context of a fractionated, dose-escalation dosing regimen may result in a reduction (e.g., by 20% or greater, 25% or greater, 30% or greater, 35% or greater, 40% or greater, 45% or greater, 50% or greater, 55% or greater, 60% or greater, 65% or greater, 70% or greater, 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 96% or greater, 97% or greater, 98% or greater, or 99% or greater) or complete inhibition (100% reduction) of undesirable events, such as cytokine-driven toxicities (e.g., cytokine release syndrome (CRS)), infusion-related reactions (IRRs), macrophage activation syndrome (MAS), neurologic toxicities, severe tumor lysis syndrome (TLS), neutropenia, thrombocytopenia, elevated liver enzymes, and/or central nervous system (CNS) toxicities, following treatment with a bispecific anti-FcRH5/anti-CD3 antibody using the fractionated, dose-escalation dosing regimen of the invention relative to treatment with a bispecific anti-FcRH5/anti-CD3 antibody using an non-fractionated dosing regimen.

F. Safety and Efficacy

i. Safety

[0419] In some aspects, less than 15% (e.g., less than 14%, less than 13%, less than 12%, less than 11%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1%) of patients treated using the methods described herein experience Grade 3 or Grade 4 cytokine release syndrome (CRS). In some aspects, less than 5% of patients treated using the methods described herein experience Grade 3 or Grade 4 CRS.

[0420] In some aspects, less than 10% (e.g., less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1%) of patients treated using the methods described herein experience Grade 4+ CRS. In some aspects, less than 3% of patients treated using the methods described herein experience Grade 4+ CRS. In some aspects, no patients experience Grade 4+ CRS.

[0421] In some aspects, less than 10% (e.g., less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1%) of patients treated using the methods described herein experience Grade 3 CRS. In some aspects, less than 5% of patients treated using the methods described herein experience Grade 3 CRS. In some aspects, no patients experience Grade 3 CRS. In some aspects, Grade 2+ CRS events occur only in the first cycle of treatment. In some aspects, Grade 2 CRS events occur only in the first cycle of treatment. In some aspects, Grade 2 CRS events do not occur.

[0422] In some aspects, less than 3% of patients treated using the methods described herein experience Grade 4+ CRS, less than 5% of patients treated using the methods described herein experience Grade 3 CRS, and Grade 2+ CRS events occur only in the first cycle of treatment.

[0423] In some aspects, no Grade 3+ CRS events occur and Grade 2 CRS events occur only in the first cycle of treatment.

[0424] In some aspects, symptoms of immune effector cell-associated neurotoxicity syndrome (ICANS) are limited to confusion, disorientation, and expressive aphasia and resolve with steroids.

[0425] In some aspects, less than 10% (e.g., less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less

than 4%, less than 3%, less than 2%, or less than 1%) of patients treated using the methods described herein experience seizures or other Grade 3+ neurologic adverse events. In some aspects, less than 5% of patients experience seizures or other Grade 3+ neurologic adverse events. In some aspects, no patients experience seizures or other Grade 3+ neurologic adverse events.

[0426] In some aspects, all neurological symptoms are either self-limited or resolved with steroids and/or tocilizumab therapy.

ii. Efficacy

[0427] In some aspects, the overall response rate (ORR) for patients treated using the methods described herein is at least 25%, e.g., is at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100%. In some aspects, the ORR is at least 40%. In some aspects, the ORR is at least 45% (e.g., at least 45%, 45.5%, 46%, 46.5%, 47%, 47.5%, 48%, 48.5%, 49%, 49.5%, or 50%) at least 55%, or at least 65%. In some aspects, the ORR is at least 47.2%. In some aspects, the ORR is about 47.2%. In some aspects, the ORR is 75% or greater. In some aspects, at least 1% of patients (e.g., at least 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of patients) have a complete response (CR) or a very good partial response (VGPR). In some aspects, the ORR is 40%-50%, and 10%-20% of patients have a CR or a VGPR. In some aspects, the ORR is at least 40%, and at least 20% of patients have a CR or a VGPR.

[0428] In some aspects, the average duration of response (DoR) for patients treated using the methods described herein is at least two months, e.g., at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, at least one year, or more than one year. In some aspects, the average DoR is at least four months. In some aspects, the average DoR is at least five months. In some aspects, the average DoR is at least seven months.

[0429] In some aspects, the six month progression-free survival (PFS) rate for patients treated using the methods described herein is at least 10%, e.g., is at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100%. In some aspects, the six month PFS rate is at least 25%. In some aspects, the six month PFS rate is at least 40%. In some aspects, the six month PFS rate is at least 55%.

G. Methods of Administration

[0430] The methods and treatments may involve administering the bispecific anti-FcRH5/anti-CD3 antibody, the lenalidomide, and/or any additional therapeutic agent by any suitable means, including parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intravenous, subcutaneous, intramuscular, intraarterial, and intraperito-

neal administration routes. In some embodiments, the bispecific anti-FcRH5/anti-CD3 antibody is administered by intravenous infusion. In other instances, the bispecific anti-FcRH5/anti-CD3 antibody is administered subcutaneously. In some instances, the bispecific anti-FcRH5/anti-CD3 antibody administered by intravenous injection exhibits a less toxic response (i.e., fewer unwanted effects) in a patient than the same bispecific anti-FcRH5/anti-CD3 antibody administered by subcutaneous injection, or vice versa.

[0431] In some aspects, the bispecific anti-FcRH5/anti-CD3 antibody is administered intravenously over 4 hours (± 15 minutes), e.g., the first dose of the antibody is administered over 4 hours ± 15 minutes.

[0432] In some aspects, the first dose and the second dose of the antibody are administered intravenously with a median infusion time of less than four hours (e.g., less than three hours, less than two hours, or less than one hour) and further doses of the antibody are administered intravenously with a median infusion time of less than 120 minutes (e.g., less than 90 minutes, less than 60 minutes, or less than 30 minutes).

[0433] In some aspects, the first dose and the second dose of the antibody are administered intravenously with a median infusion time of less than three hours and further doses of the antibody are administered intravenously with a median infusion time of less than 90 minutes.

[0434] In some aspects, the first dose and the second dose of the antibody are administered intravenously with a median infusion time of less than three hours and further doses of the antibody are administered intravenously with a median infusion time of less than 60 minutes. In some aspects, the patient is hospitalized (e.g., hospitalized for 72 hours, 48 hours, 24 hours, or less than 24 hours) during one or more administrations of the anti-FcRH5/anti-CD3 antibody, e.g., hospitalized for the C1D1 (cycle 1, dose 1) or the C1D1 and the C1D2 (cycle 1, dose 2). In some aspects, the patient is hospitalized for 72 hours following administration of the C1D1 and the C1D2. In some aspects, the patient is hospitalized for 24 hours following administration of the C1D1 and the C1D2. In some aspects, the patient is not hospitalized following the administration of any dose of the anti-FcRH5/anti-CD3 antibody.

[0435] For all the methods described herein, the bispecific anti-FcRH5/anti-CD3 antibody, lenalidomide, and/or any additional therapeutic agent(s) would be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The bispecific anti-FcRH5/anti-CD3 antibody, lenalidomide, and/or any additional therapeutic agent(s) need not be, but is optionally formulated with, one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of the bispecific anti-FcRH5/anti-CD3 antibody, lenalidomide, and/or any additional therapeutic agent(s) present in the formulation, the type of disorder or treatment, and other factors discussed above. The bispecific anti-FcRH5/anti-CD3 antibody, lenalidomide, and/or any additional therapeutic agent(s) may be suitably administered to the patient over a series of treatments.

H. Anti-FcRH5/Anti-CD3 Bispecific Antibodies

[0436] The methods described herein include administering to a subject having a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM (e.g., an MM with a high-risk cytogenetic feature)))) a bispecific antibody that binds to FcRH5 and CD3 (i.e., a bispecific anti-FcRH5/anti-CD3 antibody). Any suitable bispecific antibody that binds to FcRH5 and CD3 (i.e., a bispecific anti-FcRH5/anti-CD3 antibody) may be used.

[0437] In some instances, any of the methods described herein may include administering a bispecific antibody that includes an anti-FcRH5 arm having a first binding domain comprising at least one, two, three, four, five, or six hyper-variable regions (HVRs) selected from (a) an HVR-H1 comprising the amino acid sequence of RFGVH (SEQ ID NO: 1); (b) an HVR-H2 comprising the amino acid sequence of VIWRGGSTDYNAAFVS (SEQ ID NO: 2); (c) an HVR-H3 comprising the amino acid sequence of HYYGSSDYALDN (SEQ ID NO: 3); (d) an HVR-L1 comprising the amino acid sequence of KASQDVRLNLVV (SEQ ID NO: 4); (e) an HVR-L2 comprising the amino acid sequence of SGSYRYS (SEQ ID NO: 5); and (f) an HVR-L3 comprising the amino acid sequence of QQHYSPPYT (SEQ ID NO: 6). In some instances, the bispecific anti-FcRH5/anti-CD3 antibody comprises at least one (e.g., 1, 2, 3, or 4) of the heavy chain framework regions FR-H1, FR-H2, FR-H3, and FR-H4 comprising the sequences of SEQ ID NOS: 17-20, respectively, and/or at least one (e.g., 1, 2, 3, or 4) of the light chain framework regions FR-L1, FR-L2, FR-L3, and FR-L4 comprising the sequences of SEQ ID NOS: 21-24, respectively.

[0438] In some instances, any of the methods described herein may include administering a bispecific antibody that includes an anti-FcRH5 arm having a first binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of RFGVH (SEQ ID NO: 1); (b) an HVR-H2 comprising the amino acid sequence of VIWRGGSTDYNAAFVS (SEQ ID NO: 2); (c) an HVR-H3 comprising the amino acid sequence of HYYGSSDYALDN (SEQ ID NO: 3); (d) an HVR-L1 comprising the amino acid sequence of KASQDVRLNLVV (SEQ ID NO: 4); (e) an HVR-L2 comprising the amino acid sequence of SGSYRYS (SEQ ID NO: 5); and (f) an HVR-L3 comprising the amino acid sequence of QQHYSPPYT (SEQ ID NO: 6). In some instances, the bispecific anti-FcRH5/anti-CD3 antibody comprises at least one (e.g., 1, 2, 3, or 4) of the heavy chain framework regions FR-H1, FR-H2, FR-H3, and FR-H4 comprising the sequences of SEQ ID NOS: 17-20, respectively, and/or at least one (e.g., 1, 2, 3, or 4) of the light chain framework regions FR-L1, FR-L2, FR-L3, and FR-L4 comprising the sequences of SEQ ID NOS: 21-24, respectively.

[0439] In some instances, the bispecific antibody comprises an anti-FcRH5 arm comprising a first binding domain comprising (a) a heavy chain variable (VH) domain comprising an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 7; (b) a light chain variable (VL) domain comprising an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 8; or (c) a VH domain as in (a) and a VL domain as in (b). Accordingly, in some instances, the first binding domain comprises a VH domain comprising

an amino acid sequence of SEQ ID NO: 7 and a VL domain comprising an amino acid sequence of SEQ ID NO: 8.

[0440] In some instances, any of the methods described herein may include administering a bispecific anti-FcRH5/anti-CD3 antibody that includes an anti-CD3 arm having a second binding domain comprising at least one, two, three, four, five, or six HVRs selected from (a) an HVR-H1 comprising the amino acid sequence of SYYIH (SEQ ID NO: 9); (b) an HVR-H2 comprising the amino acid sequence of WIYPENDNTKYNEKFKD (SEQ ID NO: 10); (c) an HVR-H3 comprising the amino acid sequence of DGYSRYYFDY (SEQ ID NO: 11); (d) an HVR-L1 comprising the amino acid sequence of KSSQSLNSRTKNYLA (SEQ ID NO: 12); (e) an HVR-L2 comprising the amino acid sequence of WTSTRKS (SEQ ID NO: 13); and (f) an HVR-L3 comprising the amino acid sequence of KQSFILRT (SEQ ID NO: 14). In some instances, the anti-FcRH5/anti-CD3 bispecific antibody comprises at least one (e.g., 1, 2, 3, or 4) of heavy chain framework regions FR-H1, FR-H2, FR-H3, and FR-H4 comprising the sequences of SEQ ID NOs: 25-28, respectively, and/or at least one (e.g., 1, 2, 3, or 4) of the light chain framework regions FR-L1, FR-L2, FR-L3, and FR-L4 comprising the sequences of SEQ ID NOs: 29-32, respectively.

[0441] In some instances, any of the methods described herein may include administering a bispecific anti-FcRH5/anti-CD3 antibody that includes an anti-CD3 arm having a second binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SYYIH (SEQ ID NO: 9); (b) an HVR-H2 comprising the amino acid sequence of WIYPENDNTKYNEKFKD (SEQ ID NO: 10); (c) an HVR-H3 comprising the amino acid sequence of DGYSRYYFDY (SEQ ID NO: 11); (d) an HVR-L1 comprising the amino acid sequence of KSSQSLNSRTKNYLA (SEQ ID NO: 12); (e) an HVR-L2 comprising the amino acid sequence of WTSTRKS (SEQ ID NO: 13); and (f) an HVR-L3 comprising the amino acid sequence of KQSFILRT (SEQ ID NO: 14). In some instances, the anti-FcRH5/anti-CD3 bispecific antibody comprises at least one (e.g., 1, 2, 3, or 4) of heavy chain framework regions FR-H1, FR-H2, FR-H3, and FR-H4 comprising the sequences of SEQ ID NOs: 25-28, respectively, and/or at least one (e.g., 1, 2, 3, or 4) of the light chain framework regions FR-L1, FR-L2, FR-L3, and FR-L4 comprising the sequences of SEQ ID NOs: 29-32, respectively.

[0442] In some instances, the bispecific antibody comprises an anti-CD3 arm comprising a second binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 15; (b) a VL domain comprising an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 16; or (c) a VH domain as in (a) and a VL domain as in (b). Accordingly, in some instances, the second binding domain comprises a VH domain comprising an amino acid sequence of SEQ ID NO: 15 and a VL domain comprising an amino acid sequence of SEQ ID NO: 16.

[0443] In some instances, any of the methods described herein may include administering a bispecific antibody that includes (1) an anti-FcRH5 arm having a first binding domain comprising at least one, two, three, four, five, or six

HVRs selected from (a) an HVR-H1 comprising the amino acid sequence of RFGVH (SEQ ID NO: 1); (b) an HVR-H2 comprising the amino acid sequence of VIWRGGSTDYNAAFVS (SEQ ID NO: 2); (c) an HVR-H3 comprising the amino acid sequence of HYYGSSDYALDN (SEQ ID NO: 3); (d) an HVR-L1 comprising the amino acid sequence of KASQDVRNLVV (SEQ ID NO: 4); (e) an HVR-L2 comprising the amino acid sequence of SGGSYRYS (SEQ ID NO: 5); and (f) an HVR-L3 comprising the amino acid sequence of QQHYSPPYT (SEQ ID NO: 6) and (2) an anti-CD3 arm having a second binding domain comprising at least one, two, three, four, five, or six HVRs selected from (a) an HVR-H1 comprising the amino acid sequence of SYYIH (SEQ ID NO: 9); (b) an HVR-H2 comprising the amino acid sequence of WIYPENDNTKYNEKFKD (SEQ ID NO: 10); (c) an HVR-H3 comprising the amino acid sequence of DGYSRYYFDY (SEQ ID NO: 11); (d) an HVR-L1 comprising the amino acid sequence of KSSQSLNSRTKNYLA (SEQ ID NO: 12); (e) an HVR-L2 comprising the amino acid sequence of WTSTRKS (SEQ ID NO: 13); and (f) an HVR-L3 comprising the amino acid sequence of KQSFILRT (SEQ ID NO: 14).

[0444] In some instances, any of the methods described herein may include administering a bispecific antibody that includes (1) an anti-FcRH5 arm having a first binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of RFGVH (SEQ ID NO: 1); (b) an HVR-H2 comprising the amino acid sequence of VIWRGGSTDYNAAFVS (SEQ ID NO: 2); (c) an HVR-H3 comprising the amino acid sequence of HYYGSSDYALDN (SEQ ID NO: 3); (d) an HVR-L1 comprising the amino acid sequence of KASQDVRNLVV (SEQ ID NO: 4); (e) an HVR-L2 comprising the amino acid sequence of SGGSYRYS (SEQ ID NO: 5); and (f) an HVR-L3 comprising the amino acid sequence of QQHYSPPYT (SEQ ID NO: 6) and (2) an anti-CD3 arm having a second binding domain comprising the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SYYIH (SEQ ID NO: 9); (b) an HVR-H2 comprising the amino acid sequence of WIYPENDNTKYNEKFKD (SEQ ID NO: 10); (c) an HVR-H3 comprising the amino acid sequence of DGYSRYYFDY (SEQ ID NO: 11); (d) an HVR-L1 comprising the amino acid sequence of KSSQSLNSRTKNYLA (SEQ ID NO: 12); (e) an HVR-L2 comprising the amino acid sequence of WTSTRKS (SEQ ID NO: 13); and (f) an HVR-L3 comprising the amino acid sequence of KQSFILRT (SEQ ID NO: 14).

[0445] In some instances, the anti-FcRH5/anti-CD3 bispecific antibody comprises (1) at least one (e.g., 1, 2, 3, or 4) of heavy chain framework regions FR-H1, FR-H2, FR-H3, and FR-H4 comprising the sequences of SEQ ID NOs: 17-20, respectively, and/or at least one (e.g., 1, 2, 3, or 4) of the light chain framework regions FR-L1, FR-L2, FR-L3, and FR-L4 comprising the sequences of SEQ ID NOs: 21-24, respectively, and (2) at least one (e.g., 1, 2, 3, or 4) of heavy chain framework regions FR-H1, FR-H2, FR-H3, and FR-H4 comprising the sequences of SEQ ID NOs: 25-28, respectively, and/or at least one (e.g., 1, 2, 3, or 4) of the light chain framework regions FR-L1, FR-L2, FR-L3, and FR-L4 comprising the sequences of SEQ ID NOs: 29-32, respectively. In some instances, the anti-FcRH5/anti-CD3 bispecific antibody comprises (1) all four of heavy chain framework regions FR-H1, FR-H2, FR-H3, and FR-H4 comprising the sequences of SEQ ID NOs:

17-20, respectively, and/or all four of the light chain framework regions FR-L1, FR-L2, FR-L3, and FR-L4 comprising the sequences of SEQ ID NOs: 21-24, respectively, and (2) all four of heavy chain framework regions FR-H1, FR-H2, FR-H3, and FR-H4 comprising the sequences of SEQ ID NOs: 25-28, respectively, and/or all four (e.g., 1, 2, 3, or 4) of the light chain framework regions FR-L1, FR-L2, FR-L3, and FR-L4 comprising the sequences of SEQ ID NOs: 29-32, respectively.

[0446] In some instances, the anti-FcRH5/anti-CD3 bispecific antibody comprises (1) an anti-FcRH5 arm comprising a first binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 7; (b) a VL domain comprising an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 8; or (c) a VH domain as in (a) and a VL domain as in (b), and (2) an anti-CD3 arm comprising a second binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 15; (b) a VL domain comprising an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 16; or (c) a VH domain as in (a) and a VL domain as in (b). In some instances, the anti-FcRH5/anti-CD3 bispecific antibody comprises (1) a first binding domain comprising a VH domain comprising an amino acid sequence of SEQ ID NO: 7 and a VL domain comprising an amino acid sequence of SEQ ID NO: 8 and (2) a second binding domain comprising a VH domain comprising an amino acid sequence of SEQ ID NO: 15 and a VL domain comprising an amino acid sequence of SEQ ID NO: 16.

[0447] In some instances, the anti-FcRH5/anti-CD3 bispecific antibody comprises an anti-FcRH5 arm comprising a heavy chain polypeptide (H1) and a light chain polypeptide (L1), wherein (a) H1 comprises an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 35 and/or (b) L1 comprises an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 36.

[0448] In some instances, the anti-FcRH5/anti-CD3 bispecific antibody comprises an anti-FcRH5 arm comprising a heavy chain polypeptide (H1) and a light chain polypeptide (L1), wherein (a) H1 comprises the amino acid sequence of SEQ ID NO: 35 and/or (b) L1 comprises the amino acid sequence of SEQ ID NO: 36. In some instances, the anti-FcRH5/anti-CD3 bispecific antibody comprises an anti-CD3 arm comprising a heavy chain polypeptide (H2) and a light chain polypeptide (L2), wherein (a) H2 comprises an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 37 and/or (b) L2 comprises an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%,

94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 38.

[0449] In some instances, the anti-FcRH5/anti-CD3 bispecific antibody comprises an anti-CD3 arm comprising a heavy chain polypeptide (H2) and a light chain polypeptide (L2), wherein (a) H2 comprises the amino acid sequence of SEQ ID NO: 37; and (b) L2 comprises the amino acid sequence of SEQ ID NO: 38. In some instances, the anti-FcRH5/anti-CD3 bispecific antibody comprises an anti-FcRH5 arm comprising a heavy chain polypeptide (H1) and a light chain polypeptide (L1) and an anti-CD3 arm comprising a heavy chain polypeptide (H2) and a light chain polypeptide (L2), and wherein (a) H1 comprises an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 35; (b) L1 comprises an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 36; (c) H2 comprises an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 37; and (d) L2 comprises an amino acid sequence having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to, or the sequence of, SEQ ID NO: 38.

[0450] In some instances, the anti-FcRH5/anti-CD3 bispecific antibody comprises an anti-FcRH5 arm comprising a heavy chain polypeptide (H1) and a light chain polypeptide (L1) and an anti-CD3 arm comprising a heavy chain polypeptide (H2) and a light chain polypeptide (L2), and wherein (a) H1 comprises the amino acid sequence of SEQ ID NO: 35; (b) L1 comprises the amino acid sequence of SEQ ID NO: 36; (c) H2 comprises the amino acid sequence of SEQ ID NO: 37; and (d) L2 comprises the amino acid sequence of SEQ ID NO: 38.

[0451] In some instances, the anti-FcRH5/anti-CD3 bispecific antibody is cevostamab.

[0452] In some instances, the anti-FcRH5/anti-CD3 bispecific antibody according to any of the above embodiments described above may incorporate any of the features, singly or in combination, as described in Sections 1-7 below.

1. Antibody Affinity

[0453] In certain embodiments, an antibody provided herein has a dissociation constant (K_D) of $\leq 1 \mu\text{M}$, $\leq 250 \text{ nM}$, $\leq 100 \text{ nM}$, $\leq 15 \text{ nM}$, $\leq 10 \text{ nM}$, $\leq 6 \text{ nM}$, $\leq 4 \text{ nM}$, $\leq 2 \text{ nM}$, $\leq 1 \text{ nM}$, $\leq 0.1 \text{ nM}$, $\leq 0.01 \text{ nM}$, or $\leq 0.001 \text{ nM}$ (e.g., 10^{-8} M or less, e.g., from 10^{-8} M to 10^{-13} M , e.g., from 10^{-9} M to 10^{-13} M).

[0454] In one embodiment, K_D is measured by a radiolabeled antigen binding assay (RIA). In one embodiment, an RIA is performed with the Fab version of an antibody of interest and its antigen. For example, solution binding affinity of Fabs for antigen is measured by equilibrating Fab with a minimal concentration of (^{125}I)-labeled antigen in the presence of a titration series of unlabeled antigen, then capturing bound antigen with an anti-Fab antibody-coated plate (see, e.g., Chen et al., *J. Mol. Biol.* 293:865-881 (1999)). To establish conditions for the assay, MICROTITER® multi-well plates (Thermo Scientific) are coated overnight with 5 g/ml of a capturing anti-Fab antibody (Cappel Labs) in 50 mM sodium carbonate (pH 9.6), and subsequently blocked with 2% (w/v) bovine serum albumin

in PBS for two to five hours at room temperature (approximately 23° C.). In a non-adsorbent plate (Nunc #269620), 100 pM or 26 PM [^{125}I]-antigen are mixed with serial dilutions of a Fab of interest (e.g., consistent with assessment of the anti-VEGF antibody, Fab-12, in Presta et al., *Cancer Res.* 57:4593-4599 (1997)). The Fab of interest is then incubated overnight; however, the incubation may continue for a longer period (e.g., about 65 hours) to ensure that equilibrium is reached. Thereafter, the mixtures are transferred to the capture plate for incubation at room temperature (e.g., for one hour). The solution is then removed and the plate washed eight times with 0.1% polysorbate 20 (TWEEN-20TM) in PBS. When the plates have dried, 150 μl /well of scintillant (MICROSCINT-20TM; Packard) is added, and the plates are counted on a TOP-COUNTTM gamma counter (Packard) for ten minutes. Concentrations of each Fab that give less than or equal to 20% of maximal binding are chosen for use in competitive binding assays.

[0455] According to another embodiment, K_D is measured using a BIACORE[®] surface plasmon resonance assay. For example, an assay using a BIACORE[®]-2000 or a BIACORE[®]-3000 (BIAcore, Inc., Piscataway, NJ) is performed at 37° C. with immobilized antigen CM5 chips at ~10 response units (RU). In one embodiment, carboxymethylated dextran biosensor chips (CM5, BIACORE, Inc.) are activated with N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) and N-hydroxysuccinimidate (NHS) according to the supplier's instructions. Antigen is diluted with 10 mM sodium acetate, pH 4.8, to 5 $\mu\text{g}/\text{ml}$ (~0.2 μM) before injection at a flow rate of 5 $\mu\text{l}/\text{minute}$ to achieve approximately 10 response units (RU) of coupled protein. Following the injection of antigen, 1 M ethanolamine is injected to block unreacted groups. For kinetics measurements, two-fold serial dilutions of Fab (0.78 nM to 500 nM) are injected in PBS with 0.05% polysorbate 20 (TWEEN-20TM) surfactant (PBST) at 37° C. at a flow rate of approximately 25 $\mu\text{l}/\text{min}$. Association rates (K_{on} , or k_a) and dissociation rates (K_{off} , or k_d) are calculated using a simple one-to-one Langmuir binding model (BIACORE[®] Evaluation Software version 3.2) by simultaneously fitting the association and dissociation sensograms. The equilibrium dissociation constant (K_D) is calculated as the ratio K_{off}/K_{on} . See, for example, Chen et al., *J. Mol. Biol.* 293:865-881 (1999). If the on-rate exceeds 106 $\text{M}^{-1}\text{s}^{-1}$ by the surface plasmon resonance assay above, then the on-rate can be determined by using a fluorescent quenching technique that measures the increase or decrease in fluorescence emission intensity (excitation=295 nm; emission=340 nm, 16 nm band-pass) at 37° C. of a 20 nM anti-antigen antibody (Fab form) in PBS, pH 7.2, in the presence of increasing concentrations of antigen as measured in a spectrometer, such as a stop-flow equipped spectrophotometer (Aviv Instruments) or a 8000-series SLM-AMINCOTM spectrophotometer (ThermoSpectronic) with a stirred cuvette.

2. Antibody Fragments

[0456] In certain embodiments, an antibody provided herein (e.g., an anti-FcRH5/anti-CD3 TDB) is an antibody fragment that binds FcRH5 and CD3. Antibody fragments include, but are not limited to, Fab, Fab', Fab'-SH, F(ab')₂, Fv, and scFv fragments, and other fragments described below. For a review of certain antibody fragments, see Hudson et al. *Nat. Med.* 9:129-134 (2003). For a review of

scFv fragments, see, e.g., Pluckthun, in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenburg and Moore eds., (Springer-Verlag, New York), pp. 269-315 (1994); see also WO 93/16185; and U.S. Pat. Nos. 5,571,894 and 5,587,458. For discussion of Fab and F(ab')₂ fragments comprising salvage receptor binding epitope residues and having increased in vivo half-life, see U.S. Pat. No. 5,869,046.

[0457] Diabodies are antibody fragments with two antigen-binding sites that may be bivalent or bispecific. See, for example, EP 404,097; WO 1993/01161; Hudson et al. *Nat. Med.* 9:129-134 (2003); and Hollinger et al. *Proc. Natl. Acad. Sci. USA* 90:6444-6448 (1993). Triabodies and tetraabodies are also described in Hudson et al. *Nat. Med.* 9:129-134 (2003).

[0458] Single-domain antibodies are antibody fragments comprising all or a portion of the heavy chain variable domain or all or a portion of the light chain variable domain of an antibody. In certain embodiments, a single-domain antibody is a human single-domain antibody (Domantis, Inc., Waltham, MA; see, e.g., U.S. Pat. No. 6,248,516 B1).

[0459] Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody as well as production by recombinant host cells (e.g., *E. coli* or phage), as described herein.

3. Chimeric and Humanized Antibodies

[0460] In certain embodiments, an antibody provided herein (e.g., an anti-FcRH5/anti-CD3 TDB) is a chimeric antibody. Certain chimeric antibodies are described, e.g., in U.S. Pat. No. 4,816,567; and Morrison et al. *Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984)). In one example, a chimeric antibody comprises a non-human variable region (e.g., a variable region derived from a mouse, rat, hamster, rabbit, or non-human primate, such as a monkey) and a human constant region. In a further example, a chimeric antibody is a “class switched” antibody in which the class or subclass has been changed from that of the parent antibody. Chimeric antibodies include antigen-binding fragments thereof.

[0461] In certain embodiments, a chimeric antibody is a humanized antibody. Typically, a non-human antibody is humanized to reduce immunogenicity to humans, while retaining the specificity and affinity of the parental non-human antibody. Generally, a humanized antibody comprises one or more variable domains in which HVRs (or portions thereof), for example, are derived from a non-human antibody, and FRs (or portions thereof) are derived from human antibody sequences. A humanized antibody optionally will also comprise at least a portion of a human constant region. In some embodiments, some FR residues in a humanized antibody are substituted with corresponding residues from a non-human antibody (e.g., the antibody from which the HVR residues are derived), e.g., to restore or improve antibody specificity or affinity.

[0462] Humanized antibodies and methods of making them are reviewed, e.g., in Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008), and are further described, e.g., in Riechmann et al., *Nature* 332:323-329 (1988); Queen et al., *Proc. Nat'l Acad. Sci. USA* 86:10029-10033 (1989); U.S. Pat. Nos. 5,821,337, 7,527,791, 6,982,321, and 7,087,409; Kashmiri et al., *Methods* 36:25-34 (2005) (describing specificity determining region (SDR) grafting); Padlan, *Mol. Immunol.* 28:489-498 (1991) (describing “resurfacing”);

Dall'Acqua et al., *Methods* 36:43-60 (2005) (describing "FR shuffling"); and Osbourn et al., *Methods* 36:61-68 (2005) and Klimka et al., *Br. J. Cancer*, 83:252-260 (2000) (describing the "guided selection" approach to FR shuffling).

[0463] Human framework regions that may be used for humanization include but are not limited to: framework regions selected using the "best-fit" method (see, e.g., Sims et al. *J. Immunol.* 151:2296 (1993)); framework regions derived from the consensus sequence of human antibodies of a particular subgroup of light or heavy chain variable regions (see, e.g., Carter et al. *Proc. Natl. Acad. Sci. USA*, 89:4285 (1992); and Presta et al. *J. Immunol.*, 151:2623 (1993)); human mature (somatically mutated) framework regions or human germline framework regions (see, e.g., Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008)); and framework regions derived from screening FR libraries (see, e.g., Baca et al., *J. Biol. Chem.* 272:10678-10684 (1997) and Rosok et al., *J. Biol. Chem.* 271:22611-22618 (1996)).

4. Human Antibodies

[0464] In certain embodiments, an antibody provided herein (e.g., an anti-FcRH5/anti-CD3 TDB) is a human antibody. Human antibodies can be produced using various techniques known in the art. Human antibodies are described generally in van Dijk and van de Winkel, *Curr. Opin. Pharmacol.* 5:368-74 (2001) and Lonberg, *Curr. Opin. Immunol.* 20:450-459 (2008).

[0465] Human antibodies may be prepared by administering an immunogen to a transgenic animal that has been modified to produce intact human antibodies or intact antibodies with human variable regions in response to antigenic challenge. Such animals typically contain all or a portion of the human immunoglobulin loci, which replace the endogenous immunoglobulin loci, or which are present extrachromosomally or integrated randomly into the animal's chromosomes. In such transgenic mice, the endogenous immunoglobulin loci have generally been inactivated. For review of methods for obtaining human antibodies from transgenic animals, see Lonberg, *Nat. Biotech.* 23:1117-1125 (2005). See also, e.g., U.S. Pat. Nos. 6,075,181 and 6,150,584 describing XENOMOUSE™ technology; U.S. Pat. No. 5,770,429 describing HUMAB® technology; U.S. Pat. No. 7,041,870 describing K-M MOUSE® technology, and U.S. Patent Application Publication No. US 2007/0061900, describing VELOCIMOUSE® technology. Human variable regions from intact antibodies generated by such animals may be further modified, e.g., by combining with a different human constant region.

[0466] Human antibodies can also be made by hybridoma-based methods. Human myeloma and mouse-human heteromyeloma cell lines for the production of human monoclonal antibodies have been described. (See, e.g., Kozbor *J. Immunol.*, 133:3001 (1984); Brodeur et al., *Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 (Marcel Dekker, Inc., New York, 1987); and Boerner et al., *J. Immunol.*, 147:86 (1991).) Human antibodies generated via human B-cell hybridoma technology are also described in Li et al., *Proc. Natl. Acad. Sci. USA*, 103:3557-3562 (2006). Additional methods include those described, for example, in U.S. Pat. No. 7,189,826 (describing production of monoclonal human IgM antibodies from hybridoma cell lines) and Ni, *Xiandai Mianyxue*, 26 (4): 265-268 (2006) (describing human-human hybridomas). Human hybridoma technology

(Trioma technology) is also described in Vollmers and Brandlein, *Histology and Histopathology*, 20 (3): 927-937 (2005) and Vollmers and Brandlein, *Methods and Findings in Experimental and Clinical Pharmacology*, 27 (3): 185-91 (2005).

[0467] Human antibodies may also be generated by isolating Fv clone variable domain sequences selected from human-derived phage display libraries. Such variable domain sequences may then be combined with a desired human constant domain. Techniques for selecting human antibodies from antibody libraries are described below.

5. Multispecific Antibodies

[0468] In any one of the above aspects, an anti-FcRH5/anti-CD3 antibody provided herein is a multispecific antibody, for example, a bispecific antibody. Multispecific antibodies are antibodies (e.g., monoclonal antibodies) that have binding specificities for at least two different sites, e.g., antibodies having binding specificities for an immune effector cell and for a cell surface antigen (e.g., a tumor antigen, e.g., FcRH5) on a target cell other than an immune effector cell. In some aspects, one of the binding specificities is for FcRH5 and the other is for CD3.

[0469] In some aspects, the cell surface antigen may be expressed in low copy number on the target cell. For example, in some aspects, the cell surface antigen is expressed or present at less than 35,000 copies per target cell. In some embodiments, the low copy number cell surface antigen is present between 100 and 35,000 copies per target cell; between 100 and 30,000 copies per target cell; between 100 and 25,000 copies per target cell; between 100 and 20,000 copies per target cell; between 100 and 15,000 copies per target cell; between 100 and 10,000 copies per target cell; between 100 and 5,000 copies per target cell; between 100 and 2,000 copies per target cell; between 100 and 1,000 copies per target cell; or between 100 and 500 copies per target cell. Copy number of the cell surface antigen can be determined, for example, using a standard Scatchard plot.

[0470] In some embodiments, a bispecific antibody may be used to localize a cytotoxic agent to a cell that expresses a tumor antigen, e.g., FcRH5. Bispecific antibodies may be prepared as full-length antibodies or antibody fragments.

[0471] Techniques for making multispecific antibodies include, but are not limited to, recombinant co-expression of two immunoglobulin heavy chain-light chain pairs having different specificities (see Milstein and Cuello, *Nature* 305: 537 (1983)), WO 93/08829, and Traunecker et al., *EMBO J.* 10:3655 (1991)), and "knob-in-hole" engineering (see, e.g., U.S. Pat. No. 5,731,168). "Knob-in-hole" engineering of multispecific antibodies may be utilized to generate a first arm containing a knob and a second arm containing the hole into which the knob of the first arm may bind. The knob of the multispecific antibodies disclosed herein may be an anti-CD3 arm in one embodiment. Alternatively, the knob of the multispecific antibodies disclosed herein may be an anti-target/antigen arm in one embodiment. The hole of the multispecific antibodies disclosed herein may be an anti-CD3 arm in one embodiment. Alternatively, the hole of the multispecific antibodies disclosed herein may be an anti-target/antigen arm in one embodiment.

[0472] Multispecific antibodies may also be engineered using immunoglobulin crossover (also known as Fab domain exchange or CrossMab format) technology (see,

e.g., WO2009/080253; Schaefer et al., *Proc. Natl. Acad. Sci. USA*, 108:11187-11192 (2011)). Multi-specific antibodies may also be made by engineering electrostatic steering effects for making antibody Fc-heterodimeric molecules (WO 2009/089004A1); cross-linking two or more antibodies or fragments (see, e.g., U.S. Pat. No. 4,676,980, and Brennan et al., *Science*, 229:81 (1985)); using leucine zippers to produce bi-specific antibodies (see, e.g., Kostelny et al., *J. Immunol.*, 148 (5): 1547-1553 (1992)); using “diabody” technology for making bispecific antibody fragments (see, e.g., Hollinger et al., *Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993)); and using single-chain Fv (sFv) dimers (see, e.g., Gruber et al., *J. Immunol.*, 152:5368 (1994)); and preparing trispecific antibodies as described, e.g., in Tutt et al. *J. Immunol.* 147:60 (1991).

[0473] Engineered antibodies with three or more functional antigen binding sites, including “Octopus antibodies,” are also included herein (see, e.g., US 2006/0025576A1).

[0474] The antibodies, or antibody fragments thereof, may also include a “Dual Acting FAb” or “DAF” comprising an antigen binding site that binds to CD3 as well as another, different antigen (e.g., a second biological molecule) (see, e.g., US 2008/0069820).

6. Antibody Variants

[0475] In some aspects, amino acid sequence variants of the bispecific anti-FcRH5/anti-CD3 antibodies disclosed herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an antibody may be prepared by introducing appropriate modifications into the nucleotide sequence encoding the antibody, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, for example, antigen-binding.

a. Substitution, Insertion, and Deletion Variants

[0476] In certain embodiments, antibody variants having one or more amino acid substitutions are provided. Sites of interest for substitutional mutagenesis include the CDRs and FRs. Conservative substitutions are shown in Table 4 under the heading of “preferred substitutions.” More substantial changes are provided in Table 4 under the heading of “exemplary substitutions,” and as further described below in reference to amino acid side chain classes. Amino acid substitutions may be introduced into an antibody of interest and the products screened for a desired activity, for example, retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC.

TABLE 4

Exemplary and Preferred Amino Acid Substitutions		
Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys
Asn (N)	Gln; His; Asp, Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser

TABLE 4-continued

Exemplary and Preferred Amino Acid Substitutions		
Original Residue	Exemplary Substitutions	Preferred Substitutions
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine	Leu
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu

[0477] Amino acids may be grouped according to common side-chain properties:

[0478] (1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;

[0479] (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;

[0480] (3) acidic: Asp, Glu;

[0481] (4) basic: His, Lys, Arg;

[0482] (5) residues that influence chain orientation: Gly, Pro;

[0483] (6) aromatic: Trp, Tyr, Phe.

[0484] Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

[0485] One type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (e.g., a humanized or human antibody). Generally, the resulting variant(s) selected for further study will have modifications (e.g., improvements) in certain biological properties (e.g., increased affinity, reduced immunogenicity) relative to the parent antibody and/or will have substantially retained certain biological properties of the parent antibody. An exemplary substitutional variant is an affinity matured antibody, which may be conveniently generated, e.g., using phage display-based affinity maturation techniques such as those described herein. Briefly, one or more CDR residues are mutated and the variant antibodies displayed on phage and screened for a particular biological activity (e.g. binding affinity).

[0486] Alterations (e.g., substitutions) may be made in CDRs, e.g., to improve antibody affinity. Such alterations may be made in CDR “hotspots,” i.e., residues encoded by codons that undergo mutation at high frequency during the somatic maturation process (see, e.g., Chowdhury, *Methods Mol. Biol.* 207:179-196 (2008)), and/or residues that contact an antigen, with the resulting variant VH or VL being tested for binding affinity. Affinity maturation by constructing and reselecting from secondary libraries has been described, e.g., in Hoogenboom et al. in *Methods in Molecular Biology* 178:1-37 (O’Brien et al., ed., Human Press, Totowa, NJ, (2001).) In some embodiments of affinity maturation, diversity is introduced into the variable genes chosen for maturation by any of a variety of methods (e.g., error-prone PCR, chain shuffling, or oligonucleotide-directed mutagenesis). A secondary library is then created. The library is then screened to identify any antibody variants with the desired

affinity. Another method to introduce diversity involves CDR-directed approaches, in which several CDR residues (e.g., 4-6 residues at a time) are randomized. CDR residues involved in antigen binding may be specifically identified, e.g., using alanine scanning mutagenesis or modeling. CDR-H3 and CDR-L3 in particular are often targeted.

[0487] In certain embodiments, substitutions, insertions, or deletions may occur within one or more CDRs so long as such alterations do not substantially reduce the ability of the antibody to bind antigen. For example, conservative alterations (e.g., conservative substitutions as provided herein) that do not substantially reduce binding affinity may be made in CDRs. Such alterations may, for example, be outside of antigen contacting residues in the CDRs. In certain embodiments of the variant VH and VL sequences provided above, each CDR either is unaltered, or contains no more than one, two or three amino acid substitutions.

[0488] A useful method for identification of residues or regions of an antibody that may be targeted for mutagenesis is called “alanine scanning mutagenesis” as described by Cunningham and Wells (1989) *Science*, 244:1081-1085. In this method, a residue or group of target residues (e.g., charged residues such as Arg, Asp, His, Lys, and Glu) are identified and replaced by a neutral or negatively charged amino acid (e.g., alanine or polyalanine) to determine whether the interaction of the antibody with antigen is affected. Further substitutions may be introduced at the amino acid locations demonstrating functional sensitivity to the initial substitutions. Alternatively, or additionally, a crystal structure of an antigen-antibody complex to identify contact points between the antibody and antigen. Such contact residues and neighboring residues may be targeted or eliminated as candidates for substitution. Variants may be screened to determine whether they contain the desired properties.

[0489] Amino acid sequence insertions include amino-and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme (e.g., for ADEPT) or a polypeptide which increases the serum half-life of the antibody.

b. Glycosylation Variants

[0490] In certain embodiments, bispecific anti-FcRH5/anti-CD3 antibodies disclosed herein can be altered to increase or decrease the extent to which the antibody is glycosylated. Addition or deletion of glycosylation sites to anti-FcRH5 antibody of the invention may be conveniently accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or removed.

[0491] Where the antibody comprises an Fc region, the carbohydrate attached thereto may be altered. Native antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn297 of the CH2 domain of the Fc region. See, e.g., Wright et al. *TIBTECH* 15:26-32 (1997). The oligosaccharide may include various carbohydrates, e.g., mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the “stem” of the biantennary oligosaccharide structure. In some embodiments, modifications of the oli-

gosaccharide in an antibody of the invention may be made in order to create antibody variants with certain improved properties.

[0492] In one embodiment, bispecific anti-FcRH5/anti-CD3 antibody variants are provided having a carbohydrate structure that lacks fucose attached (directly or indirectly) to an Fc region. For example, the amount of fucose in such antibody may be from 1% to 80%, from 1% to 65%, from 5% to 65% or from 20% to 40%. The amount of fucose is determined by calculating the average amount of fucose within the sugar chain at Asn297, relative to the sum of all glycostructures attached to Asn 297 (e. g. complex, hybrid and high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2008/077546, for example. Asn297 refers to the asparagine residue located at about position 297 in the Fc region (EU numbering of Fc region residues); however, Asn297 may also be located about +3 amino acids upstream or downstream of position 297, i.e., between positions 294 and 300, due to minor sequence variations in antibodies. Such fucosylation variants may have improved ADCC function. See, e.g., US Patent Publication Nos. US 2003/0157108 (Presta, L.); US 2004/0093621 (Kyowa Hakko Kogyo Co., Ltd). Examples of publications related to “defucosylated” or “fucose-deficient” antibody variants include: US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US 2004/0110282; US 2004/0109865; WO 2003/085119; WO 2003/084570; WO 2005/035586; WO 2005/035778; WO2005/053742; WO2002/031140; Okazaki et al. *J. Mol. Biol.* 336:1239-1249 (2004); Yamane-Ohnuki et al. *Biotech. Bioeng.* 87:614 (2004). Examples of cell lines capable of producing defucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka et al. *Arch. Biochem. Biophys.* 249:533-545 (1986); US Pat Appl No US 2003/0157108 A1, Presta, L; and WO 2004/056312 A1, Adams et al., especially at Example 11), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, FUT8, knockout CHO cells (see, e.g., Yamane-Ohnuki et al. *Biotech. Bioeng.* 87:614 (2004); Kanda, Y. et al., *Biotechnol. Bioeng.*, 94 (4): 680-688 (2006); and WO2003/085107).

[0493] Bispecific anti-FcRH5/anti-CD3 antibody variants are further provided with bisected oligosaccharides, for example, in which a biantennary oligosaccharide attached to the Fc region of the antibody is bisected by GlcNAc. Such antibody variants may have reduced fucosylation and/or improved ADCC function. Examples of such antibody variants are described, e.g., in WO 2003/011878 (Jean-Mairet et al.); U.S. Pat. No. 6,602,684 (Umana et al.); and US 2005/0123546 (Umana et al.). Antibody variants with at least one galactose residue in the oligosaccharide attached to the Fc region are also provided. Such antibody variants may have improved CDC function. Such antibody variants are described, e.g., in WO 1997/30087 (Patel et al.); WO 1998/58964 (Raju, S.); and WO 1999/22764 (Raju, S.).

C. Fc Region Variants

[0494] In certain embodiments, one or more amino acid modifications may be introduced into the Fc region of a bispecific anti-FcRH5/anti-CD3 antibody, thereby generating an Fc region variant (see e.g., US 2012/0251531). The Fc region variant may comprise a human Fc region sequence (e.g., a human IgG1, IgG2, IgG3 or IgG4 Fc region)

comprising an amino acid modification (e.g., a substitution) at one or more amino acid positions.

[0495] In certain embodiments, the invention contemplates a bispecific anti-FcRH5/anti-CD3 antibody variant that possesses some but not all effector functions, which make it a desirable candidate for applications in which the half-life of the antibody in vivo is important, yet certain effector functions (such as complement and ADCC) are unnecessary or deleterious. In vitro and/or in vivo cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the antibody lacks FcγR binding (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express Fc (RIII only, whereas monocytes express Fc (RI, Fc (RII and Fc (RIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-492 (1991). Non-limiting examples of in vitro assays to assess ADCC activity of a molecule of interest is described in U.S. Pat. No. 5,500,362 (see, e.g., Hellstrom, et al. *Proc. Nat'l Acad. Sci. USA* 83:7059-7063 (1986)) and Hellstrom et al., *Proc. Nat'l Acad. Sci. USA* 82:1499-1502 (1985); 5,821,337 (see Bruggemann et al., *J. Exp. Med.* 166:1351-1361 (1987)). Alternatively, non-radioactive assays methods may be employed (see, for example, ACTITM non-radioactive cytotoxicity assay for flow cytometry (CellTechnology, Inc. Mountain View, CA; and Cyto Tox 96® non-radioactive cytotoxicity assay (Promega, Madison, WI). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed in vivo, e.g., in an animal model such as that disclosed in Clynes et al. *Proc. Nat'l Acad. Sci. USA* 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the antibody is unable to bind C1q and hence lacks CDC activity. See, e.g., C1q and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (see, for example, Gazzano-Santoro et al. *J. Immunol. Methods* 202: 163 (1996); Cragg et al. *Blood*. 101:1045-1052 (2003); and Cragg et al. *Blood*. 103:2738-2743 (2004)). FcRn binding and in vivo clearance/half life determinations can also be performed using methods known in the art (see, e.g., Petkova et al. *Int'l. Immunol.* 18 (12): 1759-1769 (2006)).

[0496] Antibodies with reduced effector function include those with substitution of one or more of Fc region residues 238, 265, 269, 270, 297, 327 and 329 (U.S. Pat. Nos. 6,737,056 and 8,219,149). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (U.S. Pat. Nos. 7,332,581 and 8,219,149).

[0497] In certain embodiments, the proline at position 329 of a wild-type human Fc region in the antibody is substituted with glycine or arginine or an amino acid residue large enough to destroy the proline sandwich within the Fc/Fcγ receptor interface that is formed between the proline 329 of the Fc and tryptophan residues Trp 87 and Trp 110 of FcγRIII (Sondermann et al. *Nature*. 406, 267-273, 2000). In certain embodiments, the antibody comprises at least one further amino acid substitution. In one embodiment, the further amino acid substitution is S228P, E233P, L234A,

L235A, L235E, N297A, N297D, or P331S, and still in another embodiment the at least one further amino acid substitution is L234A and L235A of the human IgG1 Fc region or S228P and L235E of the human IgG4 Fc region (see e.g., US 2012/0251531), and still in another embodiment the at least one further amino acid substitution is L234A and L235A and P329G of the human IgG1 Fc region.

[0498] Certain antibody variants with improved or diminished binding to FcRs are described. (See, e.g., U.S. Pat. No. 6,737,056; WO 2004/056312, and Shields et al., *J. Biol. Chem.* 9 (2): 6591-6604 (2001).)

[0499] In certain embodiments, an antibody variant comprises an Fc region with one or more amino acid substitutions which improve ADCC, e.g., substitutions at positions 298, 333, and/or 334 of the Fc region (EU numbering of residues).

[0500] In some embodiments, alterations are made in the Fc region that result in altered (i.e., either improved or diminished) C1q binding and/or Complement Dependent Cytotoxicity (CDC), e.g., as described in U.S. Pat. No. 6,194,551, WO 99/51642, and Idusogie et al. *J. Immunol.* 164:4178-4184 (2000).

[0501] Antibodies with increased half lives and improved binding to the neonatal Fc receptor (FcRn), which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., *J. Immunol.* 117:587 (1976) and Kim et al., *J. Immunol.* 24:249 (1994)), are described in US2005/0014934A1 (Hinton et al.). Those antibodies comprise an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn. Such Fc variants include those with substitutions at one or more of Fc region residues: 238, 256, 265, 272, 286, 303, 305, 307, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424 or 434, e.g., substitution of Fc region residue 434 (U.S. Pat. No. 7,371,826).

[0502] See also Duncan & Winter, *Nature* 322:738-40 (1988); U.S. Pat. Nos. 5,648,260; 5,624,821; and WO 94/29351 concerning other examples of Fc region variants.

[0503] In some aspects, the anti-FcRH5 and/or anti-CD3 antibody (e.g., bispecific anti-FcRH5 antibody) comprises an Fc region comprising an N297G mutation (EU numbering). In some aspects, the anti-FcRH5 arm of the bispecific anti-FcRH5 antibody comprises a N297G mutation and/or the anti-CD3 arm of the bispecific anti-FcRH5 antibody comprises an Fc region comprising an N297G mutation.

[0504] In some embodiments, the anti-FcRH5 antibody comprising the N297G mutation comprises an anti-FcRH5 arm comprising a first binding domain comprising the following six HVRs (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 1; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 2; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 3; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 4; (e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 5; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 6; and an anti-CD3 arm comprising an N297G mutation. In some embodiments, the anti-CD3 arm comprising the N297G mutation comprises the following six HVRs: (a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 9; (b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 10; (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 11; (d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 12; (e) an HVR-L2 comprising the amino

acid sequence of SEQ ID NO: 13; and (f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 14.

[0505] In some embodiments, the anti-FcRH5 antibody comprising the N297G mutation comprises an anti-FcRH5 arm comprising a first binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 7 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 8, and an anti-CD3 arm comprising an N297G mutation. In some embodiments, the anti-CD3 arm comprising the N297G mutation comprises comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 15 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 16.

[0506] In some embodiments, the anti-FcRH5 antibody comprising the N297G mutation comprises one or more heavy chain constant domains, wherein the one or more heavy chain constant domains are selected from a first CH1 (CH_1) domain, a first CH2 (CH_2) domain, a first CH3 (CH_3) domain, a second CH1 (CH_1) domain, second CH2 (CH_2) domain, and a second CH3 (CH_3) domain. In some aspects, at least one of the one or more heavy chain constant domains is paired with another heavy chain constant domain. In some aspects, the CH_3 and CH_3 domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the CH_3 domain is positionable in the cavity or protuberance, respectively, in the CH_3 domain. In some aspects, the CH_3 and CH_3 domains meet at an interface between said protuberance and cavity. In some aspects, the CH_2 and CH_2 domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the CH_2 domain is positionable in the cavity or protuberance, respectively, in the CH_2 domain. In other instances, the CH_2 and CH_2 domains meet at an interface between said protuberance and cavity. In some aspects, the anti-FcRH5 antibody is an IgG₁ antibody.

[0507] In some embodiments, the anti-FcRH5 antibody comprising the N297G mutation comprises an anti-FcRH5 arm comprising a first binding domain comprising (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 7 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 8, and an anti-CD3 arm, wherein (a) the anti-FcRH5 arm comprises T366S, L368A, Y407V, and N297G amino acid substitution mutations (EU numbering) and (b) the anti-CD3 arm comprises T366W and N297G substitution mutations (EU numbering). In some embodiments, the anti-CD3 arm comprising the T366W and N297G mutations comprises comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 15 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 16.

[0508] In other embodiments, the anti-FcRH5 antibody comprising the N297G mutation comprises an anti-FcRH5 arm comprising a first binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 7 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 8, and an anti-CD3 arm, wherein (a) the anti-FcRH5 arm comprises T366W and N297G substitution mutations (EU numbering) and (b) the anti-CD3 arm comprises T366S, L368A, Y407V, and N297G mutations (EU numbering). In some embodiments, the anti-CD3 arm comprising the N297G mutation comprises comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 15 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 16.

d. Cysteine Engineered Antibody Variants

[0509] In certain embodiments, it may be desirable to create cysteine engineered antibodies, e.g., “thioMAbs,” in which one or more residues of an antibody are substituted with cysteine residues. In particular embodiments, the substituted residues occur at accessible sites of the antibody. By substituting those residues with cysteine, reactive thiol groups are thereby positioned at accessible sites of the antibody and may be used to conjugate the antibody to other moieties, such as drug moieties or linker-drug moieties, to create an immunoconjugate, as described further herein. In certain embodiments, any one or more of the following residues may be substituted with cysteine: V205 (Kabat numbering) of the light chain; A118 (EU numbering) of the heavy chain; and S400 (EU numbering) of the heavy chain Fc region. Cysteine engineered antibodies may be generated as described, for example, in U.S. Pat. No. 7,521,541.

e. Antibody Derivatives

[0510] In certain embodiments, a bispecific anti-FcRH5/anti-CD3 antibody provided herein may be further modified to contain additional nonproteinaceous moieties that are known in the art and readily available. The moieties suitable for derivatization of the antibody include but are not limited to water soluble polymers. Non-limiting examples of water soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1,3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (e.g., glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody may vary, and if more than one polymer are attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of the antibody to be improved, whether the antibody derivative will be used in a therapy under defined conditions, etc.

[0511] In another embodiment, conjugates of an antibody and nonproteinaceous moiety that may be selectively heated by exposure to radiation are provided. In one embodiment, the nonproteinaceous moiety is a carbon nanotube (Kam et al., *Proc. Natl. Acad. Sci. USA* 102:11600-11605 (2005)). The radiation may be of any wavelength, and includes, but is not limited to, wavelengths that do not harm ordinary cells, but which heat the nonproteinaceous moiety to a temperature at which cells proximal to the antibody-nonproteinaceous moiety are killed.

7. Charged Regions

[0512] In some aspects, the binding domain that binds FcRH5 or CD3 comprises a VH1 comprising a charged region (CR₁) and a VL1 comprising a charged region (CR₂), wherein the CR₁ in the VH1 forms a charge pair with the CR₂ in the VL1. In some aspects, the CR₁ comprises a basic amino acid residue and the CR₂ comprises an acidic amino acid residue. In some aspects, the CR₁ comprises a Q39K

substitution mutation (Kabat numbering). In some aspects, the CRI consists of the Q39K substitution mutation. In some aspects, the CR₂ comprises a Q38E substitution mutation (Kabat numbering). In some aspects, the CR₂ consists of the Q38E substitution mutation. In some aspects, the second binding domain that binds CD3 comprises a VH2 comprising a charged region (CR₃) and a VL2 comprising a charged region (CR₄), wherein the CR₄ in the VL2 forms a charge pair with the CR₃ in the VH2. In some aspects, the CR₄ comprises a basic amino acid residue and the CR₃ comprises an acidic amino acid residue. In some aspects, the CR₄ comprises a Q38K substitution mutation (Kabat numbering). In some aspects, the CR₄ consists of the Q38K substitution mutation. In some aspects, the CR₃ comprises a Q39E substitution mutation (Kabat numbering). In some aspects, the VL1 domain is linked to a light chain constant domain (CL1) domain and the VH1 is linked to a first heavy chain constant domain (CH1), wherein the CL1 comprises a charged region (CR₅) and the CH1 comprises a charged region (CR₆), and wherein the CR₅ in the CL1 forms a charge pair with the CR₆ in the CH1₁. In some aspects, the CR₅ comprises a basic amino acid residue and the CR₆ comprises an acidic residue. In some aspects, the CR₅ comprises a V133K substitution mutation (EU numbering). In some aspects, the CR₅ consists of the V133K substitution mutation. In some aspects, the CR₆ comprises a S183E substitution mutation (EU numbering). In some aspects, the CR₆ consists of the S183E substitution mutation.

[0513] In other aspects, the VL2 domain is linked to a CL domain (CL2) and the VH2 is linked to a CH1 domain (CH1₂), wherein the CL2 comprises a charged region (CR₇) and the CH1₂ comprises a charged region (CR₈), and wherein the CR₇ in the CH1₂ forms a charge pair with the CR₈ in the CL2. In some aspects, the CR₇ comprises a basic amino acid residue and the CR₈ comprises an acidic amino acid residue. In some aspects, the CR₇ comprises a S183K substitution mutation (EU numbering). In some aspects, the CR₇ consists of the S183K substitution mutation. In some aspects, the CR₇ comprises a V133E substitution mutation (EU numbering). In some aspects, the CR₇ consists of the V133E substitution mutation.

[0514] In other aspects, the VL2 domain is linked to a CL domain (CL2) and the VH2 is linked to a CH1 domain (CH1₂), wherein (a) the CL2 comprises one or more mutations at amino acid residues F116, L135, S174, S176, and/or T178 (EU numbering) and (b) the CH1₂ comprises one or more mutations at amino acid residues A141, F170, S181, S183, and/or V185 (EU numbering). In some aspects, the CL2 comprises one or more of the following substitution mutations: F116A, L135V, S174A, S176F, and/or T178V. In some aspects, the CL2 comprises the following substitution mutations: F116A, L135V, S174A, S176F, and T178V. In some aspects, the CH1₂ comprises one or more of the following substitution mutations: A141I, F170S, S181M, S183A, and/or V185A. In some aspects, the CH1₂ comprises the following substitution mutations: A141I, F170S, S181M, S183A, and V185A.

[0515] In other aspects, the binding domain that binds FcRH5 or CD3 comprises a VH domain (VH1) comprising a charged region (CR₁) and a VL domain (VL1) comprising a charged region (CR₂), wherein the CR₂ in the VL₁ forms a charge pair with the CR₁ in the VH1. In some aspects, the CR₂ comprises a basic amino acid residue and the CRI

comprises an acidic amino acid residue. In some aspects, the CR₂ comprises a Q38K substitution mutation (Kabat numbering). In some aspects, the CR₂ consists of the Q38K substitution mutation. In some aspects, the CR₁ comprises a Q39E substitution mutation (Kabat numbering). In some aspects, the CR₁ consists of the Q39E substitution mutation. In some aspects, the second binding domain that binds CD3 comprises a VH domain (VH2) comprising a charged region (CR₃) and a VL domain (VL2) comprising a charged region (CR₄), wherein the CR₃ in the VH2 forms a charge pair with the CR₄ in the VL2. In some aspects, the CR₃ comprises a basic amino acid residue and the CR₄ comprises an acidic amino acid residue. In some aspects, the CR₃ comprises a Q39K substitution mutation (Kabat numbering). In some aspects, the CR₃ consists of the Q39K substitution mutation. In some aspects, the CR₄ comprises a Q38E substitution mutation (Kabat numbering). In some aspects, the CR₄ consists of the Q38E substitution mutation. In some aspects, the VL1 domain is linked to a light chain constant domain (CL1) and the VH1 is linked to a first heavy chain constant domain (CH1₁), wherein the CL1 comprises a charged region (CR₅) and the CH1₁ comprises a charged region (CR₆), and wherein the CR₅ in the CL1 forms a charge pair with the CR₆ in the CH1₁. In some aspects, the CR₅ comprises a basic amino acid residue and the CR₆ comprises an acidic residue. In some aspects, the CR₅ comprises a S183K substitution mutation (EU numbering). In some aspects, the CR₅ consists of the S183K substitution mutation. In some aspects, the CR₆ comprises a V133E substitution mutation (EU numbering). In some aspects, the CR₆ consists of the V133E substitution mutation.

[0516] In other aspects, the VL2 domain is linked to a CL domain (CL2) and the VH2 is linked to a CH1 domain (CH1₂), wherein the CL2 comprises a charged region (CR₇) and the CH1₂ comprises a charged region (CR₈), and wherein the CR₇ in the CL2 forms a charge pair with the CR₈ in the CH1₂. In some aspects, the CR₇ comprises a basic amino acid residue and the CR₈ comprises an acidic residue. In some aspects, the CR₇ comprises a V133K substitution mutation (EU numbering). In some aspects, the CR₇ consists of the V133K substitution mutation. In some aspects, the CR₈ comprises a S183E substitution mutation (EU numbering). In some aspects, the CR₈ consists of the S183E substitution mutation.

[0517] In other aspects, the VL2 domain is linked to a CL domain (CL2) and the VH2 is linked to a CH1 domain (CH1₂), wherein (a) the CL2 comprises one or more mutations at amino acid residues F116, L135, S174, S176, and/or T178 (EU numbering) and (b) the CH1₂ comprises one or more mutations at amino acid residues A141, F170, S181, S183, and/or V185 (EU numbering). In some aspects, the CL2 comprises one or more of the following substitution mutations: F116A, L135V, S174A, S176F, and/or T178V. In some aspects, the CL2 comprises the following substitution mutations: F116A, L135V, S174A, S176F, and T178V. In some aspects, the CH1₂ comprises one or more of the following substitution mutations: A141I, F170S, S181M, S183A, and/or V185A. In some aspects, the CH1₂ comprises the following substitution mutations: A141I, F170S, S181M, S183A, and V185A. In some aspects, the anti-FcRH5 antibody comprises one or more heavy chain constant domains, wherein the one or more heavy chain constant domains are selected from a first CH2 domain (CH2₁), a first CH3 domain (CH3₁), a second CH2 domain (CH2₂), and a

second CH3 domain (CH₃₂). In some aspects, at least one of the one or more heavy chain constant domains is paired with another heavy chain constant domain. In some aspects, the CH₃₁ and the CH₃₂ each comprise a protuberance (P₁) or a cavity (C₁), and wherein the P₁ or the C₁ in the CH₃₁ is positionable in the C₂ or the P₂, respectively, in the CH₃₂. In some aspects, the CH₃₁ and the CH₃₂ meet at an interface between the P₁ and the C₁. In some aspects, the CH₂₁ and the CH₂₂ each comprise (P₂) or a cavity (C₂), and wherein the P₂ or the C₂ in the CH₂₁ is positionable in the C₂ or the P₂, respectively, in the CH₂₂. In some aspects, the CH₂₁ and the CH₂₂ meet at an interface between the P₂ and the C₂.

I. Recombinant Methods and Compositions

[0518] Bispecific anti-FcRH5/anti-CD3 antibodies disclosed herein may be produced using recombinant methods and compositions, for example, as described in U.S. Pat. No. 4,816,567. In one embodiment, an isolated nucleic acid encoding an anti-FcRH5 antibody described herein is provided. Such nucleic acid may encode an amino acid sequence comprising the VL and/or an amino acid sequence comprising the VH of the antibody (e.g., the light and/or heavy chains of the antibody). In another embodiment, an isolated nucleic acid encoding an anti-CD3 antibody described herein is provided. Such a nucleic acid may encode an amino acid sequence comprising the VL and/or an amino acid sequence comprising the VH of the antibody (e.g., the light and/or heavy chains of the antibody). In a further embodiment, one or more vectors (e.g., expression vectors) comprising such a nucleic acid are provided. In a further embodiment, a host cell comprising such a nucleic acid is provided. In one such embodiment, a host cell comprises (e.g., has been transformed with): (1) a vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and an amino acid sequence comprising the VH of the antibody, or (2) a first vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and a second vector comprising a nucleic acid that encodes an amino acid sequence comprising the VH of the antibody. In one embodiment, the host cell is eukaryotic, e.g., a Chinese Hamster Ovary (CHO) cell or lymphoid cell (e.g., Y0, NS0, Sp20 cell). In one embodiment, a method of making a bispecific anti-FcRH5/anti-CD3 antibody is provided, wherein the method comprises culturing a host cell comprising a nucleic acid encoding the antibody, as provided above, under conditions suitable for expression of the antibody, and optionally recovering the antibody from the host cell (or host cell culture medium).

[0519] For recombinant production of a bispecific anti-FcRH5/anti-CD3 antibody, a nucleic acid encoding an antibody, e.g., as described above, is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

1. Two-Cell Methods for Manufacturing Bispecific Antibodies

[0520] In some aspects, an antibody disclosed herein (e.g., a bispecific anti-FcRH5/anti-CD3 antibody) is manufactured

using a method comprising two host cell lines. In some aspects, a first arm of the antibody (e.g., a first arm comprising a hole region) is produced in a first host cell line, and a second arm of the antibody (e.g., a second arm comprising a knob region) is produced in a second host cell line. The arms of the antibody are purified from the host cell lines and assembled in vitro.

2. One-Cell Methods for Manufacturing Bispecific Antibodies

[0521] In some aspects, an antibody disclosed herein (e.g., a bispecific anti-FcRH5/anti-CD3 antibody) is manufactured using a method comprising a single host cell line. In some aspects, a first arm of the antibody (e.g., a first arm comprising a hole region) and a second arm of the antibody (e.g., a second arm comprising a knob region) are produced in and purified from a single host cell line. Preferably, the first arm and the second arm are expressed at comparable levels in the host cell, e.g., are both expressed at a high level in the host cell. Similar levels of expression increase the likelihood of efficient TDB production and decrease the likelihood of light chain (LC) mispairing of TDB components. The first arm and second arm of the antibody may each further comprise amino acid substitution mutations introducing charge pairs, as described in Section IIB (7) herein. The charge pairs promote the pairing of heavy and light chain cognate pairs of each arm of the bispecific antibody, thereby minimizing mispairing.

3. Host Cells

[0522] Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells described herein. For example, antibodies may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, see, e.g., U.S. Pat. Nos. 5,648,237, 5,789,199, and 5,840,523. (See also Charlton, *Methods in Molecular Biology*, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, NJ, 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.) After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[0523] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors, including fungi and yeast strains whose glycosylation pathways have been "humanized," resulting in the production of an antibody with a partially or fully human glycosylation pattern. See Gerngross, *Nat. Biotech.* 22:1409-1414 (2004), and Li et al., *Nat. Biotech.* 24:210-215 (2006).

[0524] Suitable host cells for the expression of glycosylated antibody are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Sophoptera frugiperda* cells.

[0525] Plant cell cultures can also be utilized as hosts. See, e.g., U.S. Pat. Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES™ technology for producing antibodies in transgenic plants).

[0526] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, e.g., in Graham et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, e.g., in Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK); buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, e.g., in Mather et al., *Annals N.Y. Acad. Sci.* 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR-CHO cells (Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, e.g., Yazaki and Wu, *Methods in Molecular Biology*, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, NJ), pp. 255-268 (2003).

J. Immunoconjugates

[0527] The invention also provides immunoconjugates comprising a bispecific anti-FcRH5/anti-CD3 antibody herein conjugated to one or more cytotoxic agents, such as chemotherapeutic agents or drugs, growth inhibitory agents, toxins (e.g., protein toxins, enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof), or radioactive isotopes.

[0528] In one embodiment, an immunoconjugate is an antibody-drug conjugate (ADC) in which an antibody is conjugated to one or more drugs, including but not limited to a maytansinoid (see U.S. Pat. Nos. 5,208,020, 5,416,064 and European Patent EP 0 425 235 B1); an auristatin such as monomethylauristatin drug moieties DE and DF (MMAE and MMAF) (see U.S. Pat. Nos. 5,635,483 and 5,780,588, and 7,498,298); a dolastatin; a calicheamicin or derivative thereof (see U.S. Pat. Nos. 5,712,374, 5,714,586, 5,739,116, 5,767,285, 5,770,701, 5,770,710, 5,773,001, and 5,877,296; Hinman et al., *Cancer Res.* 53:3336-3342 (1993); and Lode et al., *Cancer Res.* 58:2925-2928 (1998)); an anthracycline such as daunomycin or doxorubicin (see Kratz et al., *Current Med. Chem.* 13:477-523 (2006); Jeffrey et al., *Bioorganic & Med. Chem. Letters* 16:358-362 (2006); Torgov et al., *Bioconj. Chem.* 16:717-721 (2005); Nagy et al., *Proc. Natl. Acad. Sci. USA* 97:829-834 (2000); Dubowchik et al., *Bioorg. & Med. Chem. Letters* 12:1529-1532 (2002); King et al., *J. Med. Chem.* 45:4336-4343 (2002); and U.S. Pat. No. 6,630,579); methotrexate; vindesine; a taxane such as docetaxel, paclitaxel, larotaxel, tesetaxel, and ortataxel; a trichothecene; and CC1065.

[0529] In another embodiment, an immunoconjugate comprises a bispecific anti-FcRH5/anti-CD3 antibody as described herein conjugated to an enzymatically active toxin or fragment thereof, including but not limited to diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), *Momordica charantia*

inhibitor, curcin, crotin, *Sapaponaria officinalis* inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the trichothecenes.

[0530] In another embodiment, an immunoconjugate comprises a bispecific anti-FcRH5/anti-CD3 antibody described herein conjugated to a radioactive atom to form a radioconjugate. A variety of radioactive isotopes are available for the production of radioconjugates. Examples include At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², Pb²¹² and radioactive isotopes of Lu. When the radioconjugate is used for detection, it may comprise a radioactive atom for scintigraphic studies, for example tc99m or 1123, or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, mri), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron.

[0531] Conjugates of an antibody and cytotoxic agent may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., *Science* 238:1098 (1987). Carbon-14-labeled 1-isothiocyanato benzyl-3-methyl diethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026. The linker may be a "cleavable linker" facilitating release of a cytotoxic drug in the cell. For example, an acid-labile linker, peptidase-sensitive linker, photolabile linker, dimethyl linker or disulfide-containing linker (Chari et al., *Cancer Res.* 52:127-131 (1992); U.S. Pat. No. 5,208,020) may be used.

[0532] The immunoconjugates or ADCs herein expressly contemplate, but are not limited to such conjugates prepared with cross-linker reagents including, but not limited to, BMPS, EMCS, GMBS, HBVS, LC-SMCC, MBS, MPBH, SBAP, SIA, SIAB, SMCC, SMPB, SMPH, sulfo-EMCS, sulfo-GMBS, sulfo-KMUS, sulfo-MBS, sulfo-SIAB, sulfo-SMCC, and sulfo-SMPB, and SVSB (succinimidyl-(4-vinylsulfone)benzoate) which are commercially available (e.g., from Pierce Biotechnology, Inc., Rockford, IL., U.S. A.).

K. Pharmaceutical Compositions and Formulations

[0533] Pharmaceutical compositions and formulations of the anti-FcRH5/anti-CD3 bispecific antibodies disclosed herein and/or lenalidomide can be prepared by mixing such antibodies having the desired degree of purity with one or more optional pharmaceutically acceptable carriers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not limited to: buffers such as L-Histidine/glacial acetic acid (e.g., at pH 5.8), phosphate, citrate, and other organic acids; tonicity agents, such

as sucrose; stabilizers, such as L-methionine; antioxidants including N-acetyl-DL-tryptophan, ascorbic acid, and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as polysorbate 20 or polyethylene glycol (PEG). Exemplary pharmaceutically acceptable carriers herein further include interstitial drug dispersion agents such as soluble neutral-active hyaluronidase glycoproteins (SHASEGP), for example, human soluble PH-20 hyaluronidase glycoproteins, such as rHuPH20 (HYLENEX®, Baxter International, Inc.). Certain exemplary SHASEGPs and methods of use, including rHuPH20, are described in US Patent Publication Nos. 2005/0260186 and 2006/0104968. In one aspect, a SHASEGP is combined with one or more additional glycosaminoglycanases such as chondroitinases.

[0534] Exemplary lyophilized antibody formulations are described in U.S. Pat. No. 6,267,958. Aqueous antibody formulations include those described in U.S. Pat. No. 6,171,586 and WO2006/044908, the latter formulations including a histidine-acetate buffer.

[0535] The formulation herein may also contain more than one active ingredients as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, it may be desirable to further provide an additional therapeutic agent (e.g., a chemotherapeutic agent, a cytotoxic agent, a growth inhibitory agent, and/or an anti-hormonal agent, such as those recited herein above). Such active ingredients are suitably present in combination in amounts that are effective for the purpose intended.

[0536] Active ingredients may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

[0537] Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, for example, films, or microcapsules.

[0538] The formulations to be used for in vivo administration are generally sterile. Sterility may be readily accomplished, e.g., by filtration through sterile filtration membranes.

III. Articles of Manufacture

[0539] In another aspect of the invention, an article of manufacture containing materials useful for the treatment, prevention, and/or diagnosis of the disorders described above is provided. The article of manufacture may comprise a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is by itself or combined with another composition effective for treating, preventing and/or diagnosing the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an anti-FcRH5/anti-CD3 bispecific antibody described herein and/or lenalidomide. In some aspects, the article of manufacture comprises at least two containers (e.g., vials), a first container holding an amount of the composition suitable for a C1D1 (cycle 1, dose 1) and a second container holding an amount of the composition suitable for a C1D2 (cycle 1, dose 2). In some aspects, the article of manufacture comprises at least three containers (e.g., vials), a first container holding an amount of the composition suitable for a C1D1, a second container holding an amount of the composition suitable for a C1D2, and a third container holding an amount of the composition suitable for a C1D3. In some aspects, the containers (e.g., vials) may be different sizes, e.g., may have sizes proportional to the amount of the composition they contain. Articles of manufacture comprising containers (e.g., vials) proportional to the intended doses may, e.g., increase convenience, minimize waste, and/or increase cost-effectiveness. The label or package insert indicates that the composition is used for treating the condition of choice (e.g., a multiple myeloma (MM), e.g., an MM with a high-risk cytogenetic feature) and further includes information related to at least one of the dosing regimens described herein. Moreover, the article of manufacture may comprise (a) a first container with a composition contained therein, wherein the composition comprises an anti-FcRH5/anti-CD3 bispecific antibody described herein; and (b) a second container with a composition contained therein, wherein the composition comprises lenalidomide. Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0540] In one aspect, provided herein is a kit for treating a subject having a cancer (e.g., a hematologic cancer (e.g., a B cell proliferative disorder (e.g., an MM))) with a high-risk cytogenetic feature, the kit comprising a bispecific antibody that binds to FcRH5 and CD3 (e.g., cevostamab) and instructions to administer the bispecific antibody to the subject in combination with lenalidomide.

[0541] In another aspect, provided herein is a kit for treating a subject having an MM with a high-risk cytogenetic feature, the kit cevostamab and instructions to administer the cevostamab to the subject cevostamab in combination with lenalidomide, wherein: (i) the subject experienced a PR or better after induction therapy; (ii) the subject has

undergone ASCT within 100 days of the onset of the method and/or has an absence of progressive disease; (iii) the cevostamab and lenalidomide are administered to the patient as a post-transplant maintenance therapy; and (iv) the high-risk cytogenetic feature comprises one or more of the following: translocation events t(4;14) or t(14;16), del(17p), or 1q gain.

[0542] In another aspect, provided herein is a kit for treating a subject having an MM with a high-risk cytogenetic feature, the kit comprising cevostamab and instructions to administer the cevostamab to the subject in combination with lenalidomide in a dosing regimen comprising: (i) a pre-phase comprising a 28-day dosing cycle (C1); (ii) a first phase, following the pre-phase, comprising a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), and a fifth dosing cycle (C5), wherein each dosing cycle of the first phase is a 28-day dosing cycle; and (iii) a second phase, following the first phase, comprising a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), a fifth dosing cycle (C5), a sixth dosing cycle (C6), and a seventh dosing cycle (C7), wherein each dosing cycle of the second phase is a 28-day dosing cycle, wherein cevostamab is administered to the subject: (i) at a first step-up dose during the pre-phase on Day 1 of the C1 and as a second step-up dose during the pre-phase on Day 8 of the C1; (ii) at a target dose during the pre-phase on Day 15 of the C1; (iii) at a target dose during the first phase on Days 1 and 15 of the C1, the C2, the C3, the C4, and the C5; and (iv) at a target dose during the second phase on Day 1 of the C1, the C2, the C3, the C4, the C5, the C6, and the C7; and wherein lenalidomide is administered to the subject: (i) during the pre-phase on Days 1-21 of the C1; (ii) during the first phase on Days 1-21 of the C1, the C2, the C3, the C4, and the C5; and (iii) during the second phase on Days 1-21 of the C1, the C2, the C3, the C4, the C5, the C6, and the C7.

[0543] In some aspects: (i) the first step-up dose of cevostamab is 0.3 mg; (ii) the second step-up dose of cevostamab is 3.6 mg; (iii) the target dose of cevostamab is between 90 mg to 198 mg, inclusive; and (iv) lenalidomide is administered at a dose of 10 mg or 15 mg.

[0544] In some aspects, the target dose is 90 mg.

[0545] In some aspects, the target dose is 132 mg.

[0546] In some aspects, the target dose is 160 mg.

IV. Example

[0547] The following are examples of the methods of the invention. It is understood that various other embodiments may be practiced, given the general description provided above, and the examples are not intended to limit the scope of the claims.

Example 1: CO43923, a Platform Study Evaluating the Safety and Efficacy of Multiple Treatment Combinations in Patients with Multiple Myeloma

[0548] Multiple myeloma (MM) remains an incurable disease, and most patients with MM relapse following frontline therapies. Patients with relapsed/refractory MM require novel effective treatment options that are able to deliver deep and durable responses in later lines of therapy to improve treatment outcomes and prolong survival. Combination regimens that target disease-associated proteins and pathways are an important part of the treatment of MM to

effectively manage the disease. Novel immunotherapies including immunomodulatory agents, bispecific antibodies, and chimeric antigen receptor T-cell therapies have shown promising anti myeloma activity as monotherapies, with preliminary data suggesting that regimens that combine these agents could further improve patient outcomes.

[0549] CO43923 is a Phase Ib/II platform study that will evaluate novel treatment combinations with new molecular entities and/or marketed products with differing mechanisms of action in individual substudies to identify early signals and establish proof-of-concept clinical data in patients with MM. The study is designed with the flexibility to open additional treatment substudies as new treatment combinations become available and to close existing treatment substudies that demonstrate unacceptable toxicity or minimal clinical activity. Concurrent non-interventional substudies will be opened to collect patient level data on standard of care (SOC) MM therapies, to capture the heterogeneity of the patient population and treatment patterns across regions in a prospective and standardized fashion. Finally, an extensive collaboration program and a preclinical/translational platform will be put in place to better understand the biology of the disease, its evolution and emerging mechanisms of treatment resistance. This will in turn inform the combinatorial strategy for the active treatment arms within the platform.

[0550] CO43923 is a platform study composed of a master study protocol and several independent substudies. The study has been designed to be fit for purpose and flexible in its development. The master study protocol outlines general information for the study, while the substudies provide specific details and requirements for the individual treatment combinations. Most substudies will be signal-seeking Phase Ib studies that will generate safety and preliminary efficacy data on treatment combinations and include a dose escalation phase to ensure optimal dosing; this will be followed by an expansion phase to better characterize the overall safety profile. An optional Phase II study will be initiated only for select combinations and will use either a single-arm design or a randomized design with a comparator. Some substudies will be non-interventional and hence will not administer active treatments but rather collect patient-level data. The first active substudy, described below, will explore the combination of cevostamab and lenalidomide as post-transplant maintenance therapy in patients with MM with high-risk cytogenetic features who experience a partial response (PR) or better after induction. The treatment arm is composed of a preliminary (dose-escalation) phase followed by an expansion phase. Patients must have completed an induction therapy and achieved a PR or better, have undergone autologous stem cell transplant (ASCT) within 100 days of first dosing in the study and harbored a high-risk cytogenetic feature at diagnosis (e.g., translocation events t(4;14) or t(14;16), del(17p), or 1q gain).

A. Objectives and Endpoints

[0551] The primary objective of this substudy is to evaluate the safety of cevostamab in combination with lenalidomide (cevostamab+lenalidomide substudy) as a maintenance treatment in patients with MM after autologous stem cell transplant (SCT) following first-line treatment. This substudy will also evaluate the pharmacokinetics, pharmacodynamics, and preliminary efficacy of cevostamab in combination with lenalidomide.

B. Study Design

i. Screening

[0552] The cevostamab+lenalidomide substudy will explore the combination of cevostamab and lenalidomide as post-transplant maintenance therapy in patients with MM with high-risk cytogenetic features who experienced at least a PR after induction. The International Myeloma Working Group (IMWG) updated criteria for diagnosis of MM can be used (see Rajkumar et al., Lancet Oncol. 15: e538-48 (2014)). All patients will receive cevostamab in combination with lenalidomide. The treatment arm is composed of a preliminary (dose-escalation) phase followed by an expansion phase, as shown in FIG. 1.

ii. Preliminary Phase: Dose Escalation

[0553] A minimum of 9 patients and a maximum of approximately 15 evaluable patients will be enrolled during the dose-escalation phase. Cohorts, each 3-6 patients, will be treated at escalating doses of cevostamab in accordance with the treatment regimens and dose-escalation rules described herein. Cevostamab starting target dose is set at 90 mg with a maximum of 132 mg.

[0554] Patients will be closely monitored for adverse events during the safety assessment window, defined as the first two cycles.

[0555] Patients who discontinue from the study prior to completing the first two cycles for reasons other than a stopping criterion will be considered non-evaluable and will be replaced. Patients who miss more than one dose of cevostamab or six doses of lenalidomide during this period for reasons other than a stopping criterion will also be considered non-evaluable and will be replaced.

[0556] After all patients have been enrolled in the dose-escalation phase and have completed the safety assessment window (two first cycles), an Internal Monitoring Committee (IMC) will be convened to review the available safety data. The IMC will also be convened if dose-limiting toxicity (DLT) criteria are met during the dose-escalation phase.

[0557] Additional cohorts may be added following the Sponsor's decision to explore the therapeutic advantage of cevostamab (e.g., change of regimen). The decision for opening such cohorts will be based on available safety and tolerability data as well as pharmacokinetic (PK) and pharmacodynamic (PD) data.

iii. Definition of Dose-Limiting Toxicity

[0558] In this treatment arm, a DLT is defined as at least one of the following events occurring during the first two cycles of treatment. The IMC will be convened if a DLT criterion is met during the dose-escalation phase and a decision to stop either further accrual or the trial in its entirety can be made.

[0559] Any Grade 5 adverse event unless unequivocally due to the underlying malignancy or another clearly identifiable cause.

[0560] Any clinically significant, non-hematologic adverse event Grade ≥ 3 unless clearly unrelated to the treatment (except fatigue, anorexia, and alopecia).

[0561] Grade 4 neutropenia lasting for >7 days despite supportive care unless clearly unrelated to the treatment.

[0562] Grade 4 thrombocytopenia lasting for >7 days despite supportive care unless clearly unrelated to the treatment.

[0563] Any case of aspartate aminotransferase (AST) or alanine aminotransferase (ALT)>3 \times upper limit of normal (ULN; if baseline was within normal limits) or baseline (if baseline was >ULN) and total bilirubin >2 \times ULN, with the following exception:

[0564] AST or ALT >3 \times ULN and total bilirubin >2 \times ULN where no individual laboratory value exceeds Grade 3 that occurs in the context of cytokine release syndrome (CRS) and resolves to Grade≤1 within <7 days.

[0565] Any Grade 4 neurologic adverse event.

[0566] Any grade seizure.

[0567] Any Grade ≥ 3 neurologic adverse event (other than seizure) that does not recover within 72 hours with appropriate management and is not considered by the investigator to be attributable to another clearly identifiable cause.

[0568] Any Grade 3 CRS not resolving within 24 hours with tocilizumab and/or corticosteroid treatment.

[0569] Any Grade 4 immune-mediated events, including CRS.

[0570] Immune-mediated events as judged by the investigator may include colitis, pneumonitis, or other events not attributable to another clearly identifiable cause.

iv. Treatment Regimens and Dose-Escalation Rules

[0571] During the dose-escalation phase, patients will be enrolled into two dose cohorts as described below.

[0572] Initially, 3 patients will be enrolled in each dose cohort, and up to an additional 6 patients can be enrolled in a cohort. A minimum of 3 patients enrolled in a cohort must complete at least the first two cycles (i.e., the DLT assessment window) before enrollment commences in the next cohort(s).

[0573] Enrollment will begin in Cohort 1 in which patients will be treated with cevostamab at a target dose of 90 mg and lenalidomide on a 28-day schedule (see FIG. 1).

[0574] Each subsequent cohort will be enrolled if allowed after a review of safety and tolerability data, as well as PK and PD data, from the first two cycles. Patients in this cohort will receive an escalated target dose of cevostamab. The step doses will remain the same as in Cohort 1. All patients will receive treatment with lenalidomide until disease progression or unacceptable toxicity and will be followed for disease progression and survival. All patients will receive treatment with cevostamab for 13 cycles or until unacceptable toxicity whichever occurs first and will be followed for disease progression and survival.

[0575] After the last patient in each cohort has completed the DLT assessment window, the next recommended dose for the subsequent cohort(s) will be determined, taking into account relevant demographic, adverse event, laboratory, dose administration, and PK (if available) data. At each dose-escalation step, the dose may be escalated or de-escalated, or an additional cohort at the same dose level may be enrolled. Two target doses, 90 mg and 132 mg, will be explored, with 90 mg being the target starting dose.

[0576] Based on a review of real-time safety data from this study and on all available data from other studies in the program, dose escalation may be halted or modified as deemed appropriate. However, 132 mg is expected to be the highest target dose tested in this substudy.

[0577] Although the DLT assessment window is defined as the first two cycles of treatment, cumulative toxicities

occurring beyond the two first cycles may be considered. At the end of the dose-escalation phase, the expansion phase for cevostamab will be decided. An expansion cohort of approximately 14 patients will then be open at that dose to collect more safety data. This expansion phase is part of Phase I of the study (e.g., see Table 5).

TABLE 5

Treatment Regimen for the Dose-Escalation Phase	
Cycle (28 days)	Dose, Route, and Regimen
Cycle 1	Cevostamab 0.3 mg intravenous (IV) on Day 1 Cevostamab 3.6 mg IV on Day 8 Cevostamab 90 mg (starting dose) IV on Day 15
Cycles 2-6	Lenalidomide 10 mg per os (PO) (by mouth) on Days 1-21 Cevostamab 90 mg (starting dose) IV on Days 1 and 15 of each cycle
Cycles 7+	Lenalidomide 10 mg PO on Days 1-21 of each cycle Cevostamab 90 mg (starting dose) IV on Day 1 of each cycle (up to cycle 13) Lenalidomide 10 mg PO on Days 1-21 of each cycle ^a

^aAfter Cycle 3, the lenalidomide dose can be increased to 15 mg at the investigator's discretion.

v. Expansion Phase

[0578] The expansion phase is designed to obtain additional safety data on cevostamab in combination with lenalidomide as well as preliminary efficacy. The expansion phase is part of Phase I of the study. Following the successful enrollment of the escalation phase and positive review by the IMC, approximately 14 patients will be enrolled in the expansion phase (e.g., see Table 6).

38:1928-37 (2020); Kaufman et al. Blood Cancer J. 10:111 (2020)) with a very poor survival benefit from single agent maintenance and a hazard ratios for death between 6 and 15 times higher than patients in the low risk category (Perrot et al., J Clin Oncol. 37:1657-65 (2019)). In a high-risk population, double agent maintenance, e.g., with cevostamab and

lenalidomide as described herein, with limited overlapping toxicities, is expected to improve and deepen responses hence increasing survival while maintaining quality of life.

[0580] Cevostamab monotherapy has demonstrated an acceptable safety profile and shown efficacy in patients with R/R MM. As of November 2021, two studies are ongoing to confirm the safety and efficacy of cevostamab in this patient population. As such, combination with lenalidomide is

TABLE 6

Treatment Regimen for the Expansion Phase	
Cycle (28 days)	Dose, Route, and Regimen
Cycle 1	Cevostamab 0.3 mg IV on Day 1 Cevostamab 3.6 mg IV on Day 8 Cevostamab to be determined (TBD) mg IV on Day 15
Cycles 2-6	Lenalidomide 10 mg PO on Days 1-21 Cevostamab TBD mg IV on Days 1 and 15 of each cycle
Cycles 7+	Lenalidomide 10 mg PO on Days 1-21 of each cycle Cevostamab TBD mg IV on Day 1 of each cycle up to Cycle 13 Lenalidomide 10 mg PO on Days 1-21 of each cycle ^a

^aAfter Cycle 3, the lenalidomide dose can be increased to 15 mg at the investigator's discretion.

vi. Rationale for Treatment Combination and Study Population

[0579] There is no curative treatment for MM, and almost all patients will eventually relapse. Lenalidomide is the only drug approved as maintenance treatment after autologous SCT to delay relapse and extend survival. In 2017, a meta-analysis of three randomized controlled trials (CALGB100104, RV-MM-PI-209, and IFM2005-02) showed a statistically significant increase in progression-free survival (PFS) as well as overall survival (OS) with lenalidomide maintenance between the two groups (active vs. control) (McCarthy et al., J Clin Oncol. 35:3279-89 (2017)). So far, maintenance treatment is usually given as monotherapy, and patients with cytogenetic low risk features derive survival benefit. However, patients with cytogenetic high-risk features remain a high-unmet medical need (Nooka et al., Leukemia 28:690-3 (2014); Gay et al., Blood 136 (Suppl 1): 35-7 (2020); Joseph et al., J Clin Oncol.

expected to deepen and prolong response in patients in remission on the following basis:

[0581] FcRH5 is a cell-surface antigen whose expression is restricted to cells of the B lineage, including plasma cells. It is expressed with 100% prevalence on MM samples tested to date (Elkins et al., Mol Cancer Ther. 11:2222-32 (2012); Li et al., Cancer Cell 31:383-95 (2017)).

[0582] Nonclinical studies have demonstrated that cevostamab is broadly active in cell killing in multiple human MM cell lines and primary human MM plasma cells with a wide range of FcRH5 expression levels, including cells with minimal FcRH5 expression, suggesting that even very low levels of FcRH5 expression may be sufficient for clinical activity (Li et al., Cancer Cell 31:383-95 (2017)).

[0583] Preliminary findings from Study GO39775 (ClinicalTrials.gov) indicate that patients are able to

achieve an objective response to cevostamab treatment regardless of baseline FcRH5 expression. Clinical response has been observed in patients with the lowest FcRH5 expression.

vii. Rationale for Cevostamab Dose

[0584] The dose of cevostamab used in this study is based on data from Study GO39775 where double step-up dosing at a first step-up dose of 0.3 mg, a second step-up dose of 3.6 mg, and a target dose at 160 mg (i.e., 0.3/3.6/160 mg) has been shown to be safe and effective at inducing a response in patients with R/R MM. The dosing schedule has been modified from a 21-day cycle to a 28-day cycle to accommodate lenalidomide dosing and to ease patient treatment burden. Cevostamab target dose of a maximum of 132 mg every two weeks (Q2W) is equivalent to 160 mg every three weeks (Q3W), a dose that has been found to be safe in Study GO39775. A lower target dose of 90 mg Q2W will be the starting point of dose escalation towards 132 mg. These doses have been selected based on the full body of evidence available across cevostamab studies, considering PD, PK, safety, and efficacy data.

viii. Rationale for Lenalidomide Dose

[0585] Lenalidomide will be administered at 10 mg per day on Days 1-21 per standard of care. This dose can be increased to 15 mg after three cycles at the investigator's discretion as per standard of care.

ix. Outcome Measures

[0586] Outcome measures will be broken into primary and secondary outcome measures. Primary and secondary outcome measures, as well as the time frame for evaluating outcomes, are outlined in Table 7 below.

TABLE 7

Outcome Measures	
Outcome Measure	Time Frame
Primary Outcome Measures	
Percentage of participants with adverse events (AEs)	Baseline up to approximately 5 years
Percentage of participants with DLTs	Baseline up to approximately 5 years
Percentage of participants with CRS	Baseline up to approximately 5 years
Rate of very good partial response (VGPR) or better	Baseline up to approximately 5 years
Secondary Outcome Measures	
Conversion to a better response - From PR to VGPR or better, or from VGPR to complete response (CR) or stringent complete response (sCR)	Up to approximately 5 years
PFS	Start of study treatment to first date of disease progression or death from any cause, whichever occurs first (up to approximately 5 years)
OS	Up to approximately 5 years
Minimal residual disease (MRD) negativity rate	Up to approximately 5 years
Objective response rate (ORR)	Baseline up to approximately 5 years
CR or sCR	Up to approximately 5 years
Duration of response (DOR)	Up to approximately 5 years
Time to first response	Up to approximately 5 years
Time to best response	Up to approximately 5 years
Maximum concentration observed (C_{max})	Up to approximately 5 years
Minimum concentration under steady-state conditions within a dosing interval (C_{min})	Up to approximately 5 years
Time to maximum concentration (T_{max})	Up to approximately 5 years
Area under the concentration-time curve (AUC)	Up to approximately 5 years
Total clearance of drug (CL)	Up to approximately 5 years
Volume of distribution at steady state	Up to approximately 5 years

C. Materials and Methods

i. Patients

[0587] Approximately 3 to 18 patients with MM will be enrolled in the preliminary phase (dose escalation). Up to 14 patients with MM will be enrolled in the expansion phase in order to reach at least 20 patients at the chosen dose for this phase.

ii. Inclusion Criteria

[0588] Patients must meet the following inclusion criteria for the CO43823 study:

[0589] Age ≥ 18 years at time of signing Informed Consent Form.

[0590] Ability to comply with the study protocol, in the investigator's judgment.

[0591] Diagnosed with MM per IMWG criteria.

[0592] Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2.

[0593] Resolution of adverse events from prior anti-cancer therapy to Grade≤1, with the following exceptions:

[0594] Any grade alopecia is allowed.

[0595] Peripheral sensory or motor neuropathy must have resolved to Grade≤2.

[0596] Agreement to undergo scheduled assessments and procedures, including bone marrow biopsy and aspirate, as detailed in the respective substudies.

[0597] Laboratory values as follows:

[0598] Hepatic function

[0599] AST and ALT≤3× upper limit of normal (ULN)

- [0600] Total bilirubin \leq 1.5 \times ULN
- [0601] Patients with a documented history of Gilbert syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible.
- [0602] Hematologic function (requirement prior to first dose of study treatment)
- [0603] Platelet count \geq 50,000/mm³ without transfusion support within 7 days prior to first dose
- [0604] ANC \geq 1000/mm³ without granulocyte colony-stimulating factor support
- [0605] Total hemoglobin \geq 8 g/dl
- [0606] Creatinine \leq 2.0 mg/dl and creatinine clearance \geq 30 mL/min (either calculated using modified Cockcroft-Gault equation or per 24-hour urine collection)
- [0607] Patients must meet the following criteria for entry in the cevostamab+lenalidomide substudy:
- [0608] Completion of planned induction therapy and achievement of at least a PR.
- [0609] ASCT within 100 days prior to first study treatment and the absence of progressive disease.
- [0610] Cytogenetic high-risk features at diagnosis:
- [0611] Translocation events: t(4;14), t(14;16) (IMWG criteria; Rajkumar et al., Lancet Oncol. 15: e538-48 (2014)).
- [0612] Del (17p) (IMWG criteria; Rajkumar et al., Lancet Oncol. 15: e538-48 (2014)).
- [0613] Gain in chromosome 1q.
- [0614] Agreement to comply with all local requirements of the lenalidomide risk minimization plan, which includes the global pregnancy prevention program.
- [0615] For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception.
- [0616] For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom even if they have had a prior vasectomy, and agreement to refrain from donating sperm.
- iii. Exclusion Criteria
- [0617] Patients who meet any of the following criteria will be excluded from entry in the cevostamab+lenalidomide substudy:
- [0618] Inability to comply with protocol-mandated hospitalization and procedures.
- [0619] History of confirmed progressive multifocal leukoencephalopathy.
- [0620] History of other malignancy within 2 years prior to screening.
- [0621] Current or past history of central nervous system (CNS) disease.
- [0622] Significant cardiovascular disease that may limit a participant's ability to adequately respond to a CRS event.
- [0623] Symptomatic active pulmonary disease or requiring supplemental oxygen.
- [0624] Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection at study enrollment, or any major episode of infection requiring treatment with IV antibiotics where the last dose of IV antibiotics was given within 14 days prior to first study treatment.
- [0625] Known or suspected chronic active Epstein-Barr virus (EBV) infection.
- [0626] Positive serologic or PCR test results for acute or chronic hepatitis B virus (HBV) infection.
- [0627] Acute or chronic hepatitis C virus (HCV) infection.
- [0628] Known history of HIV seropositivity.
- [0629] Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation that such a live, attenuated vaccine will be required during the study.
- [0630] Any medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the participant's safe participation in and completion of the study, or which could affect compliance with the protocol or interpretation of results.
- [0631] Severe hypersensitivity reactions to lenalidomide.
- [0632] History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
- [0633] Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
- [0634] History of erythema multiforme, Grade \geq 3 rash, or blistering following prior treatment with immunomodulatory derivatives.
- [0635] Pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the final dose of study treatment.
- iv. Study Treatment, Other Treatments Relevant to the Study Design, Dosage, and Administration
- [0636] The investigational medicinal products (IMPs) for the cevostamab+lenalidomide substudy are cevostamab, tocerizumab, and lenalidomide. Protocol-specified premedications are considered non-investigational medicinal products.
- [0637] Treatment in both the dose-escalation phase and the expansion phase will be administered as detailed in Table 5 and Table 6 until patients experience unacceptable toxicity or disease progression, as determined by the investigator. Cevostamab will be administered for a maximum of 13 cycles.
- V. Cevostamab
- [0638] Cevostamab will be administered as a fixed dose independent of body weight. Cevostamab will be administered to patients by IV infusion using standard IV bags where applicable. Compatibility testing has shown that cevostamab is stable in extension sets. The drug product will be delivered by IV bag infusion, with a final cevostamab volume determined by the dose.
- [0639] During Cycle 1, patients will be hospitalized for a minimum of 48 hours after each infusion of cevostamab.
- [0640] Cevostamab will be administered in a setting with immediate access to trained critical care personnel and facilities equipped to respond to and manage medical emergencies. Cevostamab dosing will occur only if a patient's clinical assessment and/or laboratory test values are acceptable.

[0641] All cevostamab doses will be administered to well-hydrated patients. Corticosteroid premedication (dexamethasone 20 mg IV preferred, alternative corticosteroid equivalent such as methylprednisolone 80 mg IV is also acceptable) must be administered 1 hour prior to the administration of each cevostamab dose as follows:

[0642] All doses in Cycles 1 and 2.

[0643] In Cycles 3 and beyond: only if the patient experienced CRS with the prior dose.

[0644] In addition, premedication with oral acetaminophen or paracetamol (e.g., 500-1000 mg) and 25-50 mg diphenhydramine will be administered prior to administration of all cevostamab doses, unless contraindicated. For sites that do not have access to diphenhydramine, an equivalent medication may be substituted per local practice.

[0645] Initially, cevostamab will be administered over 4 hours (+15 minutes). The infusion may be slowed or interrupted for patients experiencing IRRs and/or CRS. At the end of the cevostamab infusions during Cycle 1, patients will be hospitalized. Patients will be observed at least 90 minutes for fever, chills, rigors, hypotension, nausea, or other signs and symptoms of IRRs following each subsequent cevostamab infusion. In the absence of IRRs and CRS after receiving the first target dose, the infusion time of cevostamab in subsequent cycles may be reduced to 2 hours. If repeat step-up dosing is required, the next two doses (step-up and target dose) will be administered over 4 hours.

[0646] Patients who receive less than 80% of the cevostamab step-up dose may repeat the step-up dose (if the patient meets all the dosing requirements) prior to receiving the higher target dose. A repeat step-up dose will be allowed if a patient experiences an adverse event during a step-up dose that the investigator determines to be clinically significant and warrants a repeat step-up dose at the next dosing. The step-up dose will be repeated for any patient that experiences a Grade ≥ 3 CRS following a step-up dose prior to receiving the first target dose.

vi. Tocilizumab

[0647] Tocilizumab will be administered as a rescue IMP when necessary to patients who experience a CRS event. Tocilizumab will be administered for the treatment of CRS when necessary, as described herein.

vii. Lenalidomide

[0648] Lenalidomide will be provided as 5- and 10-mg capsules. Lenalidomide should be stored at room temperature away from direct sunlight and should be protected from excessive heat and cold. Lenalidomide will be administered at a dose 10 mg by mouth once daily on Days 1-21 of a 28-day cycle with an option to increase to 15 mg.

[0649] Lenalidomide capsules should be swallowed whole with water and should not be broken, chewed, or opened. The capsules may be taken with or without food.

[0650] On the days when lenalidomide and cevostamab are administered, lenalidomide should be given first, followed by the cevostamab infusion. Lenalidomide should be administered at approximately the same time each day. If a dose of lenalidomide is missed and it has been ≤ 12 hours since the time of the scheduled dose, the patient may take the missed dose. If it has been >12 hours, the dose should be skipped and the next dose should be taken at the regularly scheduled time. Two doses should not be taken at the same time. If a dose is vomited, the dose should not be re-taken.

viii. Response Criteria

[0651] The efficacy analyses specific to the cevostamab+lenalidomide substudy will assess the improvement of treatment response (e.g., from PR to CR), PFS, and OS, as well as proportion of patients with minimal residual disease negativity. Treatment response can be assessed as described below in Table 8.

[0652] ORR is defined as the proportion of patients with a sCR, CR, VGPR, or PR on two consecutive occasions. ORR point estimate will be calculated by treatment arm, along with the 90% CIs (Clopper-Pearson exact method). Patients without postbaseline assessments will be considered as non-responders.

TABLE 8

International Myeloma Working Group Uniform Response Criteria (2016)	
Response Subcategory	Response Criteria
All response categories require two consecutive assessments made any time before starting any new therapy.	
Stringent complete response (sCR)	CR as defined below, plus: Normal FLC ratio and absence of clonal cells in bone marrow (BM) by immunohistochemistry (kappa/lambda ratio $\leq 4:1$ or $\geq 1:2$ for kappa and lambda patients, respectively after counting ≥ 100 plasma cells). ^a
Complete response (CR)	No evidence of initial monoclonal protein isotype(s) on immunofixation of the serum and urine, ^b disappearance of any soft tissue plasmacytomas, and $\leq 5\%$ plasma cells in BM.
Very good partial response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis; or $\geq 90\%$ reduction in serum M-protein plus urine M-protein level <100 mg/24 hr. For patients achieving very good partial response by other criteria, a soft tissue plasmacytoma must decrease by more than 90% in the sum of the maximal perpendicular diameter (SPD) compared with baseline.
Partial Response (PR)	$\geq 50\%$ reduction of serum M-protein and reduction in 24 hr urinary M-protein by $\geq 90\%$ or to <200 mg/24 hr. If the serum and urine M-protein are unmeasurable, a $\geq 50\%$ decrease in the difference between involved and unininvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable and serum FLC assay is also unmeasurable, $\geq 50\%$ reduction in plasma cells is required in place of M-protein, provided baseline BM plasma cell percentage was $\geq 30\%$. In addition to the above listed criteria, if present at baseline, a $\geq 50\%$ reduction in the size (SPD) ^c of soft tissue plasmacytomas is also required.

TABLE 8-continued

International Myeloma Working Group Uniform Response Criteria (2016)	
Response Subcategory	Response Criteria
All response categories require two consecutive assessments made any time before starting any new therapy.	
Minimal response (MR)	≥25% but ≤49% reductions of serum M-protein and reduction in 24-hr urine M-protein by 50%-89%. In addition to the above criteria, if present at baseline, 25%-49% reduction in the size (SPD) ^c of soft tissue plasmacytomas is also required.
Stable Disease (SD)	Not meeting criteria for sCR, CR, VGPR, PR, MR, or PD.
Progressive disease (PD) ^{d, e}	Any increase of ≥25% from lowest response value in any one of the following: Serum M-protein (absolute increase must be ≥0.5 g/dL) Serum M-protein increase ≥1 g/dL, if the lowest M component was ≤5 g/dL Urine M-protein (absolute increase must be ≥200 mg/24 hr) In patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) In patients without measurable serum and urine M-protein levels and without measurable disease by FLC: BM plasma cell percentage irrespective of baseline status (absolute % must be ≥10%) ^b Appearance of new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis ≥50% increase in circulating plasma cells (minimum 200 cells per microliter) if this is the only measure of disease.
Clinical relapse	Requires one or more of the following: Direct indications of increasing disease and/or end organ dysfunction (CRAB features) ^f related to the underlying clonal plasma cell proliferative disorder. It is not used in calculation of time to progression or PFS but is listed here as something that can be reported optionally or for use in clinical practice. Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression). Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion. Hypercalcemia >11 mg/dl (2.65 mmol/L) Decrease in hemoglobin of ≥2 g/dl (1.25 mmol/L) not related to therapy or other non-myeloma related conditions Rise in serum creatinine by 2 mg/dL or more (177 µmol/L or more) from the start of therapy and attributable to myeloma Hyperviscosity related to serum paraprotein.
Relapse from CR (to be used only if the endpoint studied is disease-free survival) ^c	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ≥5% plasma cells in the BM Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia).

BM = bone marrow; CR = complete response; CT = computed tomography; FDG-PET = fluorodeoxyglucose positron emission tomography; FLC = free light chain; M-protein = monoclonal immunoglobulin protein; MR = minimal response; MRI = magnetic resonance imaging; PD = progressive disease; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; SD = stable disease; SPD = sum of the product of diameters; VGPR = very good partial response.

Note:

Patients should be categorized as having stable disease until they meet criteria for any response category or have progressive disease. Patients will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; patients cannot move to a lower response category. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

^a Special attention should be given to the emergence of a different M-protein following treatment, especially in the setting of patients having achieved a conventional CR, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of IgGk in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

^b In some cases it is possible that the original M-protein light-chain isotype is still detected on immunofixation but the accompanying heavy-chain component has disappeared; this would not be considered a CR even though the heavy-chain component is not detectable, since it is possible that the clone evolved to one that secreted only light chains. Thus, if a patient has IgA lambda myeloma, then to qualify as CR there should be no IgA detectable on serum or urine immunofixation; if free lambda is detected without IgA, then it must be accompanied by a different heavy-chain isotype (IgG, IgM, etc.). Modified from Durie et al. 2006. This requires two consecutive assessments to be carried out at any time before the institution of any new therapy (Durie et al. 2015).

^c Plasmacytoma measurements should be taken from the CT portion of the FDG-PET/CT or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, the skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD. Any soft tissue plasmacytoma documented at baseline must undergo serial monitoring; otherwise, the patient is classified as not evaluable.

^d Positive immunofixation alone in a patient previously classified as achieving a CR will not be considered progression. Criteria for relapse from a CR should be used only when calculating disease-free survival.

^e In the case where a value is felt to be a spurious result per investigator discretion (e.g., a possible laboratory error), that value will not be considered when determining the lowest value.

^f CRAB features = calcium elevation, renal failure, anemia, lytic bone lesions.

SEQUENCE LISTING

[0653] Table 9 shows sequences that are used throughout the application.

TABLE 9

<u>Sequence Listing</u>	
SEQ ID NO:	SEQUENCE
SEQ ID NO: 1	RFGVH
SEQ ID NO: 2	VIWRGGSTDYNAAFVS
SEQ ID NO: 3	HYYGSSDYALDN
SEQ ID NO: 4	KASQDVRNLVV
SEQ ID NO: 5	SGSYRYS
SEQ ID NO: 6	QQHYSPPYT
SEQ ID NO: 7	EVOLVESGPGLVKPSETSLTCTVSGFSLTRFGVHWVROPPGKGLEWLGVIRGGSTDYNAAFV SRLTISKDN SKNQVSLKLSSVTAADTAVYYCSNHYYGSSDYALDNWGQGTLVTVSS
SEQ ID NO: 8	DIQMTQSPSSL SASVGDRVTITCKASQDVRNLV VWFQQKPGKAPKLLIYSGSYRYSGVPSRFSG SGSGTDFLTLSLQPEDFATYYCQQHYSPPYTFGQGTKVEIK
SEQ ID NO: 9	SYYIH
SEQ ID NO: 10	WIYPENDNTKYNEKFKD
SEQ ID NO: 11	DGYSRYYFDY
SEQ ID NO: 12	KSSQSLLNSRTRKNYLA
SEQ ID NO: 13	WTSTRKS
SEQ ID NO: 14	KQSFILRT
SEQ ID NO: 15	EVQLVQSGAEVKKPGASVKVSCKASGFTFTSYYIHWVRQAPGQGLEWIGWIYPENDNTKYNEKF KDRVTITADTSTSTAYLELSSLRSEDTAVYYCARDGYSRYYFDYWGQGTLVTVSS
SEQ ID NO: 16	DIVMTQSPDSLAVSLGERATINC KSSQSLNSRTRKNYLA WYQOKPGQSPKLLIYWTSTRKSGV PDRFSGSGSGTDFTLTISLQAEDVA VYYCQSFILRTFGQGTKVEIK
SEQ ID NO: 17	EVQLVESGPGLVKPSETSLTCTVSGFSLT
SEQ ID NO: 18	WVRQAPPGKGLEWLG
SEQ ID NO: 19	RLTISKDN SKNQVSLKLSSVTAADTAVYYCSN
SEQ ID NO: 20	WGQGTLVTVSS
SEQ ID NO: 21	DIQMTQSPSSL SASVGDRVTITC
SEQ ID NO: 22	WFQQKPGKAPKLLIY
SEQ ID NO: 23	GVPSRFSGSGSGTDFTLTISLQPEDFATYYC
SEQ ID NO: 24	FGQGTKVEIK
SEQ ID NO: 25	EVQLVQSGAEVKKPGASVKVSCKASGFTFT
SEQ ID NO: 26	WVRQAPGQGLEWIG
SEQ ID NO: 27	RVTITADTSTSTAYLELSSLRSEDTAVYYCAR
SEQ ID NO: 28	WGQGTLVTVSS
SEQ ID NO: 29	DIVMTQSPDSLAVSLGERATINC
SEQ ID NO: 30	WYQQKPGQSPKLLIY
SEQ ID NO: 31	GVPDRFSGSGSGTDFTLTISLQAEDVA VYYC
SEQ ID NO: 32	FGQGTKVEIK

TABLE 9-continued

-continued

RFGVH

5

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source
1..16
mol_type = protein
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SEQ ID NO: 3      moltype = AA length = 12
FEATURE
source
1..12
mol_type = protein
organism = synthetic construct

SEQUENCE: 3
HYYGSSDYAL DN                                12

SEQ ID NO: 4      moltype = AA length = 11
FEATURE
source
1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 4
KASQDVRNLV V                                11

SEQ ID NO: 5      moltype = AA length = 7
FEATURE
source
1..7
mol_type = protein
organism = synthetic construct

SEQUENCE: 5
SGSYRYS                                7

SEQ ID NO: 6      moltype = AA length = 9
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source
1..9
mol_type = protein
organism = synthetic construct

SEQUENCE: 6
QQHYSPPYT                                9

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SEQ ID NO: 8      moltype = AA length = 107
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organism = synthetic construct

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RFGSGSGSTD FTLTISSLQP EDFATYYCQQ HYSPPYTFCQ GTKVEIK                107

SEQ ID NO: 9      moltype = AA length = 5
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1..5
mol_type = protein
organism = synthetic construct

SEQUENCE: 9
SYYIH                                5

SEQ ID NO: 10     moltype = AA length = 17
FEATURE
source
1..17
mol_type = protein
organism = synthetic construct

SEQUENCE: 10
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-continued

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	organism = synthetic construct
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SEQ ID NO: 17	moltype = AA length = 30
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	mol_type = protein	
	organism = synthetic construct	
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	organism = synthetic construct	
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	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 27		
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	mol_type = protein
	organism = synthetic construct
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SEQ ID NO: 32	moltype = AA length = 10
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	mol_type = protein
	organism = synthetic construct
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	mol_type = genomic DNA
	organism = Homo sapiens
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1-115. (canceled)

116. A method of treating a subject having a multiple myeloma (MM) with a high-risk cytogenetic feature, the method comprising administering to the subject (i) a bispecific antibody that binds to fragment crystallizable receptor-like 5 (FcRH5) and cluster of differentiation 3 (CD3) and (ii) lenalidomide, wherein the bispecific antibody comprises an anti-FcRH5 arm comprising a first binding domain comprising the following six hypervariable regions (HVRs):

- (a) an HVR-H1 comprising the amino acid sequence of RFGVH (SEQ ID NO: 1);
- (b) an HVR-H2 comprising the amino acid sequence of VIWRGGSTDYNAAFVS (SEQ ID NO: 2);
- (c) an HVR-H3 comprising the amino acid sequence of HYYGSSDYALDN (SEQ ID NO:3);
- (d) an HVR-L1 comprising the amino acid sequence of KASQDVRNLVV (SEQ ID NO: 4);
- (e) an HVR-L2 comprising the amino acid sequence of SGSYRYS (SEQ ID NO: 5); and
- (f) an HVR-L3 comprising the amino acid sequence of QQHYSPPYT (SEQ ID NO: 6), and

an anti-CD3 arm comprising a second binding domain comprising the following six HVRs:

- (a) an HVR-H1 comprising the amino acid sequence of SYYIH (SEQ ID NO: 9);
- (b) an HVR-H2 comprising the amino acid sequence of WIYPENDNTKYNEFKD (SEQ ID NO: 10);
- (c) an HVR-H3 comprising the amino acid sequence of DGYSRYYFDY (SEQ ID NO: 11);

(d) an HVR-L1 comprising the amino acid sequence of KSSQSLLNSRTRKNYLA (SEQ ID NO: 12);

(e) an HVR-L2 comprising the amino acid sequence of WTSTRKS (SEQ ID NO: 13); and

(f) an HVR-L3 comprising the amino acid sequence of KQSFILRT (SEQ ID NO: 14).

117. The method of claim **116**, wherein:

- (a) the subject has experienced a partial response (PR) or better after induction therapy;
- (b) the subject has undergone autologous stem cell transplantation (ASCT) within 100 days of the onset of the method and/or has an absence of progressive disease;
- (c) the subject harbored the high-risk cytogenetic feature at the time of diagnosis of MM;
- (d) the high-risk cytogenetic feature comprises one or more of the following: translocation events t(4;14) or t(14;16), del(17p), or 1q gain;
- (e) the bispecific antibody and lenalidomide are administered to the patient as a post-transplant maintenance therapy; and/or
- (f) the bispecific antibody and the lenalidomide are administered to the subject in a dosing regimen comprising:
 - (i) a first phase comprising one or more dosing cycles, wherein the first phase comprises administering the bispecific antibody to the subject every two weeks (Q2W); and

(ii) a second phase comprising one or more dosing cycles, wherein the second phase comprises administering the bispecific antibody to the subject every four weeks (Q4W).

118. The method of claim 117, wherein:

- (a) each dosing cycle of the first phase and/or the second phase of the dosing regimen is a 28-day dosing cycle; and/or
- (b) the dosing regimen further comprises a pre-phase, prior to the first phase, comprising one or more dosing cycles, wherein:
 - (i) each dosing cycle of the pre-phase is a 28-day dosing cycle;
 - (ii) the pre-phase comprises at least one dosing cycle (C1); and
 - (iii) the pre-phase comprises administering the bispecific antibody to the subject every week (QW).

119. The method of claim 118, wherein the pre-phase comprises administering the bispecific antibody to the subject on Days 1, 8, and 15 of the C1, and wherein:

- (a) a target dose of the bispecific antibody is administered to the subject for each administration in the pre-phase;
- (b) the pre-phase comprises administering a first step-up dose of the bispecific antibody to the subject; or
- (c) the pre-phase comprises administering a first step-up dose and a second step-up dose of the bispecific antibody to the subject.

120. The method of claim 119, wherein:

- (a) the first step-up dose is administered to the subject on Day 1 of the C1 and a target dose is administered to the subject on Days 8 and 15 of the C1; or
- (b) the first step-up dose is administered to the subject on Day 1 of C1, the second step-up dose is administered to the subject on Day 8 of the C1, and a target dose is administered to the subject on Day 15 of the C1.

121. The method of claim 120, wherein:

- (a) the first step-up dose is 3.6 mg and the target dose is 90 mg, 132 mg, or 160 mg; or
- (b) the first step-up dose is 0.3 mg, the second step-up dose is 3.6 mg, and the target dose is 90 mg, 132 mg, or 160 mg.

122. The method of claim 118, wherein:

- (a) the first phase comprises at least two dosing cycles, at least three dosing cycles, at least four dosing cycles, or at least five dosing cycles; and/or
- (b) the second phase comprises at least two dosing cycles, at least three dosing cycles, at least four dosing cycles, at least five dosing cycles, at least six dosing cycles, or at least seven dosing cycles.

123. The method of claim 122, wherein:

- (a) the first phase comprises a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), and a fifth dosing cycle (C5); and/or
- (b) the second phase comprises a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), a fifth dosing cycle (C5), a sixth dosing cycle (C6), and a seventh dosing cycle (C7).

124. The method of claim 123, wherein:

- (a) the first phase comprises administering a target dose of the bispecific antibody to the subject on Days 1 and 15 of the C1, the C2, the C3, the C4, and/or the C5; and/or

(b) the second phase comprises administering a target dose of the bispecific antibody to the subject on Day 1 of the C1, the C2, the C3, the C4, the C5, the C6, and/or the C7, wherein the target dose is 90 mg, 132 mg, or 160 mg, inclusive.

125. The method of claim 118, wherein:

- (a) the bispecific antibody is administered to the subject intravenously; and/or
- (b) the lenalidomide is administered orally to the subject at a dosage of about 10 mg to about 20 mg.

126. The method of claim 125, wherein:

- (a) the lenalidomide is administered orally to the subject on Days 1-21 of each dosing cycle in the first phase and/or the second phase;
- (b) the lenalidomide is administered orally to the subject on Days 1-21 of each dosing cycle in the pre-phase; and/or
- (c) the lenalidomide is administered orally to the subject at a dosage of about 10 mg or about 15 mg.

127. The method of claim 118, wherein the method further comprises administering a corticosteroid to the subject during the first phase, during the second phase, and/or during the pre-phase.

128. The method of claim 127, wherein:

- (a) the corticosteroid is administered intravenously or orally to the subject during the first phase on Days 1 and 15 of the C1; and/or
- (b) the corticosteroid is administered intravenously or orally to the subject during the pre-phase on Days 1, 8, and 15 of the C1.

129. The method of claim 128, wherein:

- (a) the corticosteroid is administered intravenously or orally to the subject in the C2, the C3, the C4, and/or the C5 of the first phase if the subject experienced a cytokine release syndrome (CRS) event with the prior dose; and/or
- (b) the corticosteroid is administered intravenously or orally to the subject in the C1, the C2, the C3, the C4, the C5, the C6, and/or the C7 of the second phase if the subject experienced a CRS event with the prior dose.

130. The method of claim 127, wherein the corticosteroid is dexamethasone or methylprednisolone and is administered to the subject intravenously about 1 hour prior to the administration of the bispecific antibody.

131. The method of claim 130, wherein the dexamethasone is administered to the subject at a dosage of about 20 mg or the methylprednisolone is administered to the subject at a dosage of about 80 mg.

132. The method of claim 116, wherein:

- (a) the first binding domain of the anti-FcRH5 arm comprises:
 - (i) a heavy chain variable (VH) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 7,
 - (ii) a light chain variable (VL) domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 8, or
 - (iii) a VH domain as in (a) and a VL domain as in (b); and/or

- (b) the second binding domain of the anti-CD3 arm comprises:
 - (i) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 15,
 - (ii) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 16, or
 - (iii) a VH domain as in (a) and a VL domain as in (b).
- 133.** The method of claim 132, wherein:
- (a) the first binding domain comprises a VH domain comprising an amino acid sequence of SEQ ID NO: 7 and a VL domain comprising an amino acid sequence of SEQ ID NO: 8;
 - (b) the second binding domain comprises a VH domain comprising an amino acid sequence of SEQ ID NO: 15 and a VL domain comprising an amino acid sequence of SEQ ID NO: 16;
 - (c) the anti-FcRH5 arm comprises a heavy chain polypeptide (H1) and a light chain polypeptide (L1) and the anti-CD3 arm comprises a heavy chain polypeptide (H2) and a light chain polypeptide (L2), wherein:
 - (i) H1 comprises the amino acid sequence of SEQ ID NO: 35,
 - (ii) L1 comprises the amino acid sequence of SEQ ID NO: 36,
 - (iii) H2 comprises the amino acid sequence of SEQ ID NO: 37, and
 - (iv) L2 comprises the amino acid sequence of SEQ ID NO: 38; and/or
 - (d) the bispecific antibody is cevostamab.
- 134.** The method of claim 116, wherein:
- (a) the bispecific antibody comprises an aglycosylation site mutation; and/or
 - (b) the bispecific antibody is a monoclonal antibody, a humanized antibody, a chimeric antibody, or an antibody fragment that binds FcRH5 and CD3.
- 135.** The method of claim 134, wherein:
- (a) the aglycosylation site mutation reduces effector function of the bispecific antibody;
 - (b) the aglycosylation site mutation is a substitution mutation; and/or
 - (c) the antibody fragment is selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.
- 136.** The method of claim 116, wherein:
- (a) the bispecific antibody that binds to FcRH5 and CD3 is a full-length antibody;
 - (b) the bispecific antibody is an IgG antibody; and/or
 - (c) the bispecific antibody comprises one or more heavy chain constant domains, wherein the one or more heavy chain constant domains are selected from a first CH1 (CH1₁) domain, a first CH2 (CH2₁) domain, a first CH3 (CH3₁) domain, a second CH1 (CH1₂) domain, second CH2 (CH2₂) domain, and a second CH3 (CH3₂) domain.
- 137.** The method of claim 136, wherein:
- (a) the IgG antibody is an IgG₁ antibody;
 - (b) at least one of the one or more heavy chain constant domains is paired with another heavy chain constant domain;
 - (c) the CH3₁ and CH3₂ domains each comprise a protuberance or cavity, and wherein the protuberance or

- cavity in the CH3₁ domain is positionable in the cavity or protuberance, respectively, in the CH3₂ domain; and/or
 - (d) the CH2₁ and CH2₂ domains each comprise a protuberance or cavity, and wherein the protuberance or cavity in the CH2₁ domain is positionable in the cavity or protuberance, respectively, in the CH2₂ domain.
- 138.** The method of claim 137, wherein:
- (a) the CH3₁ and CH3₂ domains meet at an interface between the protuberance and cavity; and/or
 - (b) the CH2₁ and CH2₂ domains meet at an interface between said protuberance and cavity,
- wherein the anti-FcRH5 arm comprises the protuberance and the anti-CD3 arm comprises the cavity.
- 139.** The method of claim 138, wherein a CH3 domain of the anti-FcRH5 arm comprises a protuberance comprising a T366W amino acid substitution mutation (EU numbering) and a CH3 domain of the anti-CD3 arm comprises a cavity comprising T366S, L368A, and Y407V amino acid substitution mutations (EU numbering).
- 140.** The method of claim 116, wherein:
- (a) the bispecific antibody and the lenalidomide are administered to the subject concurrently with one or more additional therapeutic agents;
 - (b) the bispecific antibody and the lenalidomide are administered to the subject prior to administration of one or more additional therapeutic agents; or
 - (c) the bispecific antibody and the lenalidomide are administered to the subject subsequent to administration of one or more additional therapeutic agents.
- 141.** The method of any one of claim 140, wherein the one or more additional therapeutic agents comprises:
- (a) an effective amount of tocilizumab;
 - (b) an effective amount of a B-cell maturation antigen (BCMA)-directed therapy, an additional immunomodulator (IMiD), a CD38-directed therapy, or a combination of any of the foregoing;
 - (c) an effective amount of acetaminophen or paracetamol; and/or
 - (d) an effective amount of diphenhydramine.
- 142.** The method of claim 141, wherein:
- (a) tocilizumab is administered to the subject by intravenous infusion, wherein:
 - (i) the subject weighs ≥ 30 kg, and tocilizumab is administered to the subject at a dose of 8 mg/kg, or
 - (ii) the subject weighs <30 kg, and tocilizumab is administered to the subject at a dose of 12 mg/kg;
 - (b) tocilizumab is administered to the subject 2 hours before administration of the bispecific antibody;
 - (c) the acetaminophen or paracetamol is administered to the subject orally at a dose of between about 500 mg to about 1000 mg; and/or
 - (d) the diphenhydramine is administered to the subject orally at a dose of between about 25 mg to about 50 mg.
- 143.** The method of claim 116, wherein the subject has a CRS event, and the method further comprises treating the symptoms of the CRS event with an effective amount of tocilizumab while suspending treatment with the bispecific antibody, wherein:
- (a) the subject weighs ≥ 30 kg, and tocilizumab is intravenously administered to the subject at a dose of 8 mg/kg to treat the symptoms of the CRS event; or

(b) the subject weighs <30 kg, and tocilizumab is intravenously administered to the subject at a dose of 12 mg/kg to treat the symptoms of the CRS event.

144. A method of treating a subject having an MM with a high-risk cytogenetic feature, the method comprising administering to the subject cevostamab and lenalidomide, wherein:

- (i) the subject experienced a PR or better after induction therapy;
- (ii) the subject has undergone ASCT within 100 days of the onset of the method and/or has an absence of progressive disease;
- (iii) the cevostamab and lenalidomide are administered to the patient as a post-transplant maintenance therapy; and
- (iv) the high-risk cytogenetic feature comprises one or more of the following: translocation events t(4;14) or t(14;16), del(17p), or 1q gain.

145. A method of treating a subject having an MM with a high-risk cytogenetic feature, the method comprising administering to the subject cevostamab and lenalidomide in a dosing regimen comprising:

- (i) a pre-phase comprising a 28-day dosing cycle (C1);
- (ii) a first phase, following the pre-phase, comprising a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), and a fifth dosing cycle (C5), wherein each dosing cycle of the first phase is a 28-day dosing cycle; and

(iii) a second phase, following the first phase, comprising a first dosing cycle (C1), a second dosing cycle (C2), a third dosing cycle (C3), a fourth dosing cycle (C4), a fifth dosing cycle (C5), a sixth dosing cycle (C6), and a seventh dosing cycle (C7), wherein each dosing cycle of the second phase is a 28-day dosing cycle,

wherein cevostamab is administered to the subject:

- (i) at a first step-up dose of 0.3 mg during the pre-phase on Day 1 of the C1 and as a second step-up dose of 3.6 mg during the pre-phase on Day 8 of the C1;
- (ii) at a target dose of 90 mg, 132 mg, or 160 mg during the pre-phase on Day 15 of the C1;
- (iii) at the target dose of 90 mg, 132 mg, or 160 mg during the first phase on Days 1 and 15 of the C1, the C2, the C3, the C4, and the C5; and
- (iv) at the target dose of 90 mg, 132 mg, or 160 mg during the second phase on Day 1 of the C1, the C2, the C3, the C4, the C5, the C6, and the C7; and

wherein lenalidomide is administered to the subject at a dose of 10 mg or 15 mg:

- (i) during the pre-phase on Days 1-21 of the C1;
- (ii) during the first phase on Days 1-21 of the C1, the C2, the C3, the C4, and the C5; and
- (iii) during the second phase on Days 1-21 of the C1, the C2, the C3, the C4, the C5, the C6, and the C7.

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