

(Suntharalingam, *et al.*, Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412, NEJM 355:1018-1028 (2006)). Unfortunately, TGN1412 induced a cytokine storm, which was not predicted by toxicology studies in cynomolgus macaques or *ex vivo* human PBMC studies.

[0006] CD22 (also known as Siglec-2), a member of Siglec family, specifically recognizes α 2,6 sialic acid, and is a transmembrane protein preferentially expressed on B lymphocytes (B cells).

[0007] CD22 has a number of ascribed functions including, for example, B cell homeostasis, B cell survival and migration, dampening TLR and CD40 signaling, and inhibiting B cell receptor (BCR) signaling *via* recruitment of SH2 domain-containing phosphatases by phosphorylation of immunoreceptor tyrosine-based inhibition motifs (ITIMs) in the cytoplasmic region, as well as facilitation of adhesion between B cells and other cell types.

[0008] CD22 is not found on the surface of B cells during the early stages of development, nor is it expressed in stem cells. However, 60-70% of all B-cell lymphomas and leukemias express CD22.

[0009] An anti-CD22 antibody for treating B-cell lymphomas and leukemias has been investigated. However, the monoclonal antibody, Epratuzumab, had limited success. (Grant, *et al.* (2013) *Cancer* 119(21): 10.1002/cncr.28299)

[0010] Accordingly, there is a need in the art for improved anti-CD22-antibodies. There is also a need for anti-CD28 antibody that is safe for use in a pharmaceutical composition. Furthermore, bispecific antigen-binding molecules that bind both CD28 and a target antigen (such as CD22) would be useful in therapeutic settings in which specific targeting and T cell-mediated killing of cells that express the target antigen is desired.

SUMMARY

[0011] In a first aspect, the present disclosure refers to an isolated bispecific antigen binding molecule comprising: a) a first antigen-binding domain (D1) that binds human CD28; and b) a second antigen-binding domain (D2) that specifically binds human CD22 on a target tumor cell. The present disclosure provides bispecific antigen-binding molecules that bind CD28 and a target antigen. According to certain exemplary examples, the bispecific antigen-binding molecules bind CD28 and CD22; such bispecific antigen-binding molecules are also referred to herein as "anti-CD28/anti-CD22 bispecific molecules." The anti-CD22 portion of the anti-CD28/anti-CD22 bispecific molecule is useful for targeting cancer cells that express CD22 (*e.g.*, a cancerous B cell), and the anti-CD28 portion of the bispecific molecule is useful for activating T-cells. The simultaneous binding of CD22 on a cancer cell and CD28 on a T-cell facilitates directed killing (cell lysis) of the targeted cancer cell by the activated T-cell, *e.g.*, after TCR activation of the T cell. The anti-CD28/anti-CD22 bispecific molecules of the disclosure are therefore useful, *inter alia*, for treating diseases and disorders related to or caused by CD22-expressing tumors (*e.g.*, a B cell proliferative disorder, *e.g.*, a B cell

lymphoma, *e.g.*, diffuse large B-cell lymphoma (DLBCL, follicular lymphoma (FL), a marginal zone lymphoma).

[0012] The bispecific antigen-binding molecules according to this example of the present disclosure comprise a first antigen-binding domain that specifically binds human CD28, and a second antigen-binding domain that specifically binds CD22. The present disclosure includes anti-CD28/anti-CD22 bispecific molecules (*e.g.*, bispecific antibodies) wherein each antigen-binding domain comprises a heavy chain variable region (HCVR) paired with a light chain variable region (LCVR). In certain exemplary examples of the disclosure, the anti-CD28 antigen-binding domain and the anti-CD22 antigen binding domain each comprise different, distinct HCVRs paired with a common LCVR.

[0013] The present disclosure provides anti-CD28/anti-CD22 bispecific molecules, wherein the first antigen-binding domain that specifically binds CD28 comprises any of the HCVR amino acid sequences as set forth in Table 6. The first antigen-binding domain that specifically binds CD28 may also comprise any of the LCVR amino acid sequences as set forth in Table 6. According to certain examples, the first antigen-binding domain that specifically binds CD28 comprises any of the HCVR/LCVR amino acid sequence pairs as set forth in Table 6. The present disclosure also provides anti-CD28/anti-CD22 bispecific molecules, wherein the first antigen-binding domain that specifically binds CD28 comprises any of the heavy chain CDR1-CDR2-CDR3 amino acid sequences as set forth in Table 6, and/or any of the light chain CDR1-CDR2-CDR3 amino acid sequences as set forth in Table 6.

[0014] According to certain examples, the present disclosure provides anti-CD28/anti-CD22 bispecific molecules, wherein the first antigen-binding domain that specifically binds CD28 comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28 and 26 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0015] The present disclosure also provides anti-CD28/anti-CD22 bispecific molecules, wherein the first antigen-binding domain that specifically binds CD28 comprises a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO: 10, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. In another aspect, the present disclosure refers to an isolated bispecific antigen binding molecule that competes for binding to CD22, or binds to the same epitope on CD22 as a reference antibody, wherein the reference antibody comprises a first antigen-binding domain having an HCVR/LCVR pair comprising the amino acid sequences of SEQ ID Nos: 26/10 and a second antigen-binding domain having an HCVR/LCVR pair comprising the amino acid sequences of SEQ ID Nos: 2/10 or 18/10. In another, the present disclosure refers to an isolated bispecific antigen binding molecule that competes for binding to human CD28, or binds to the same epitope on human CD28 as a reference antibody, wherein the reference antibody comprises a first antigen-binding domain having an HCVR/LCVR pair comprising the amino acid sequences of SEQ ID NOs: 26/10 and a second antigen-binding domain having an HCVR/LCVR pair comprising the amino acid sequences of SEQ ID NOs: 2/10 or 18/10.

[0016] The present disclosure also provides anti-CD28/anti-CD22 bispecific molecules, wherein the first antigen-binding domain that specifically binds CD28 comprises a HCVR and LCVR (HCVR/LCVR) amino acid sequence pair selected from the group consisting of SEQ ID NOs: 28/10 and 26/10.

[0017] The present disclosure also provides anti-CD28/anti-CD22 bispecific molecules, wherein the first antigen-binding domain that specifically binds CD28 comprises a heavy chain CDR3 (HCDR3) domain having the amino acid sequence of SEQ ID NO: 32, or a substantially similar sequence thereto having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a light chain CDR3 (LCDR3) domain having the amino acid sequence of SEQ ID NO: 16, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0018] In certain examples, the first antigen-binding domain that specifically binds CD28 comprises the HCDR3/LCDR3 amino acid sequence pair of SEQ ID NOs: 32/16.

[0019] The present disclosure also provides anti-CD28/anti-CD22 bispecific antigen-binding molecules, wherein the first antigen-binding domain that specifically binds CD28 comprises a heavy chain CDR1 (HCDR1) domain having the amino acid sequence of SEQ ID NO: 28, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a heavy chain CDR2 (HCDR2) domain having the amino acid sequence of SEQ ID NO: 30, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a light chain CDR1 (LCDR1) domain having the amino acid sequence of SEQ ID NO: 12, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a light chain CDR2 (LCDR2) domain having the amino acid sequence of SEQ ID NO: 14, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0020] Certain non-limiting, exemplary anti-CD28/anti-CD22 bispecific antigen-binding molecules of the disclosure include a first antigen-binding domain that specifically binds CD28 comprising HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 domains, respectively, having the amino acid sequence of: SEQ ID NOs: 28-30-32-12-14-16.

[0021] The present disclosure also provides anti-CD28/anti-CD22 bispecific molecules, wherein the second antigen-binding domain that specifically binds CD22 comprises a heavy chain variable region (HCVR) having the amino acid sequence selected from the group consisting SEQ ID NOs: 2 and 18, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0022] The present disclosure also provides anti-CD28/anti-CD22 bispecific molecules, wherein the second antigen-binding domain that specifically binds CD22 comprises a light chain variable region (LCVR) having the amino acid sequence selected of SEQ ID NO: 10, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0023] The present disclosure also provides anti-CD28/anti-CD22 bispecific molecules, wherein the second antigen-binding domain that specifically binds CD22 comprises a HCVR and LCVR (HCVR/LCVR) amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10 and 18/10.

[0024] The present disclosure also provides anti-CD28/anti-CD22 bispecific molecules, wherein the second antigen-binding domain that specifically binds CD22 comprises a heavy chain CDR3 (HCDR3) domain having the amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 24, or a substantially similar sequence thereto having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a light chain CDR3 (LCDR3) domain having the amino acid sequence selected of SEQ ID NO:16, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0025] In certain examples, the second antigen-binding domain that specifically binds CD22 comprises a HCDR3/LCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOs: 8/16 and 24/16.

[0026] The present disclosure also provides anti-CD28/anti-CD22 bispecific antigen-binding molecules, wherein the second antigen-binding domain that specifically binds CD22 comprises a heavy chain CDR1 (HCDR1) domain having the amino acid sequence selected from the group consisting of SEQ ID NOs: 4 and 20, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a heavy chain CDR2 (HCDR2) domain having the amino acid sequence selected from the group consisting of SEQ ID NOs: 6 and 22, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a light chain CDR1 (LCDR1) domain having the amino acid sequence of SEQ ID NO: 12, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a light chain CDR2 (LCDR2) domain having the amino acid sequence of SEQ ID NO: 14, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0027] Certain non-limiting, exemplary anti-CD28/anti-CD22 bispecific antigen-binding molecules of the disclosure include a second antigen-binding domain that specifically binds CD22 comprising HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 domains, respectively, having the amino acid sequences selected from the group consisting of: SEQ ID NOs: 4-6-8-12-14-16 and 20-22-24-12-14-16

[0028] In a related example, the disclosure includes anti-CD28/anti-CD22 bispecific antigen binding molecules wherein the second antigen-binding domain that specifically binds CD22 comprises the heavy and light chain CDR domains contained within heavy and light chain variable region (HCVR/LCVR) sequences selected from the group consisting of SEQ ID NOs: 2/10 and 18/10.

[0029] In another aspect, the present disclosure refers to a nucleic acid molecule comprising a nucleotide sequence encoding a bispecific antibody as disclosed herein. In another example, the present disclosure provides nucleic acid molecules encoding any of the HCVR, LCVR or CDR sequences of the anti-CD28/anti-CD22 bispecific antigen-binding molecules disclosed herein, including nucleic acid molecules comprising the polynucleotide sequences as set forth in Table 7 herein, as well as nucleic acid molecules comprising two or more of the polynucleotide sequences as set forth in Table 7 in any functional combination or arrangement thereof. Recombinant expression vectors carrying the nucleic acids of the disclosure, and host cells into which such vectors have been introduced, are also encompassed by the disclosure, as are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

[0030] The present disclosure includes anti-CD28/anti-CD22 bispecific antigen-binding molecules wherein any of the aforementioned antigen-binding domains that specifically bind CD28 is combined, connected or otherwise associated with any of the aforementioned antigen binding domains that specifically bind CD22 to form a bispecific antigen-binding molecule that binds CD28 and CD22.

[0031] The present disclosure includes anti-CD28/anti-CD22 bispecific antigen-binding molecules having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or an antibody lacking a fucose moiety present on the oligosaccharide chain, for example, to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield *et al.* (2002) *JBC* 277:26733). In other

applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0032] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the bispecific antigen-binding molecule as disclosed herein, and a pharmaceutically acceptable carrier or diluent. In another example, the disclosure provides a pharmaceutical composition comprising an anti-CD28/anti-CD22 bispecific antigen-binding molecule as disclosed herein and a pharmaceutically acceptable carrier. In a related example, the disclosure features a composition which is a combination of an anti-CD28/anti-CD22 bispecific antigen-binding molecule and a second therapeutic agent. In one example, the second therapeutic agent is any agent that is advantageously combined with an anti-CD28/anti-CD22 bispecific antigen-binding molecule. Exemplary agents that may be advantageously combined with an anti-CD28/anti-CD22 bispecific antigen-binding molecule are discussed in detail elsewhere herein.

[0033] In another aspect, the present disclosure refers to an expression vector comprising the nucleic acid as disclosed herein. In another aspect, the present disclosure refers to a host cell comprising the expression vector as disclosed herein. In yet another example, the disclosure provides therapeutic methods for targeting/killing cancer cells expressing CD22 using an anti-CD28/anti-CD22 bispecific antigen-binding molecule of the disclosure, wherein the therapeutic methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an anti-CD28/anti-CD22 bispecific antigen-binding molecule of the disclosure to a subject in need thereof. In yet another aspect, the present disclosure refers to the use of an isolated bispecific antibody as disclosed herein or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for inhibiting a B-cell proliferative disorder in a subject, wherein said antibody or pharmaceutical composition is to be administered to the subject, thereby inhibiting growth of the B-cell lymphoma in the subject.

[0034] The present disclosure also includes the use of an anti-CD28/anti-CD22 bispecific antigen-binding molecule of the disclosure in the manufacture of a medicament for the treatment of a disease or disorder related to or caused by CD22 expression.

[0035] In yet another aspect, the present disclosure refers to the use of an isolated bispecific antibody as disclosed herein or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a patient suffering from B-cell proliferative disorder, or from another CD22-expressing cell malignancy, wherein said antibody or pharmaceutical composition is to be administered to the subject, thereby treating the patient suffering from a B-cell lymphoma or from another CD-22 expressing cell malignancy. In yet another example, the disclosure provides therapeutic methods for targeting/killing cancer cells expressing CD22 using an anti-CD28/anti-CD22 bispecific antigen-binding molecule of the disclosure, wherein the anti-CD28/anti-CD22 bispecific antigen-binding molecule is combined with other anti-tumor bispecific antigen-binding molecules that bind to CD3 (*e.g.*, anti-CD28/anti-CD22 combined with anti-CD3/anti-CD20 antibodies).

[0036] In still another example, the disclosure provides therapeutic methods for targeting/killing cancer cells expressing CD22 using an anti-CD28/anti-CD22 bispecific antigen-binding molecule of the disclosure, wherein the anti-CD28/anti-CD22 bispecific

antigen-binding molecule is combined with a checkpoint inhibitor targeting PD-1, PD-L1 or CTLA-4 (*e.g.*, anti-CD28/anti-CD-22 combined with anti-PD-1 antibodies). For example, in certain examples, the anti-CD28/anti-CD22 antibodies of the disclosure may be combined with agents that target PD-1, such as Pembrolizumab (Keytruda®), Nivolumab (Opdivo®), or Cemiplimab (Libtayo®). In certain examples, the anti-CD28/anti-CD22 antibodies of the disclosure may be combined with agents that target PD-L1, such as Atezolizumab (Tecentriq®), Avelumab (Bavencio®), or Durvalumab (Imfinzi®). In certain examples, the anti-CD28/anti-CD22 antibodies of the disclosure may be combined with agents that target CTLA-4, such as Ipilimumab (Yervoy®).

[0037] In still another example, the disclosure provides therapeutic methods for targeting/killing cancer cells expressing CD22 using an anti-CD28/anti-CD22 bispecific antigen-binding molecule of the disclosure, wherein the anti-CD28/anti-CD22 bispecific antigen-binding molecule is combined with other anti-tumor bispecific antigen-binding molecules that binds to CD3 (*e.g.*, anti-CD28/anti-CD22 combined with anti-CD3/anti-CD20 bispecific antibodies, for example, REGN1979 (See US9,657,102, wherein the anti-CD20 arm comprises the HCVR/LCVR amino acid pair of SEQ ID NOs: 1242/1258 and the anti-CD3 arm comprises the amino acid pair of SEQ ID NOs: 1250/1258)) and/or a checkpoint inhibitor targeting PD-1, PD-L1 or CTLA-4 (*e.g.*, anti-CD28/anti-CD22 combined with anti-PD-1 antibodies). For example, in certain examples, the anti-CD28/anti-CD22 antibodies of the disclosure may be combined with agents that target PD-1, such as Pembrolizumab (Keytruda®), Nivolumab (Opdivo®), or Cemiplimab (Libtayo®, see for example, US9,987,500, wherein cemiplimab comprises the HCVR/LCVR amino acid pair of SEQ ID NOs: 162/170)). In certain examples, the anti-CD28/anti-CD22 antibodies of the disclosure may be combined with agents that target PD-L1, such as Atezolizumab (Tecentriq®), Avelumab (Bavencio®), or Durvalumab (Imfinzi®). In certain examples, the anti-CD28/anti-CD22 antibodies of the disclosure may be combined with agents that target CTLA-4, such as Ipilimumab (Yervoy®).

[0038] Other examples will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0039] **Figure 1** is a set of graphs depicting the binding of anti-CD28/anti-CD22 bispecific antibodies to human CD4+ T-cells expressing CD28 and target cells expressing human CD22 on the cell surface.

[0040] **Figures 2A and 2B** are a set of graphs depicting that anti-CD28/anti-CD22 bispecific antibodies show increased Luciferase production in the presence of primary T-cell stimulation and CD22 target expression. **Figure 2A** is a set of graphs depicting the

activation of engineered reporter T-cells co-incubated with HEK293/hCD20, HEK293/hCD20/hCD22, or Raji/CD80 and CD86 negative cells in addition to 200pM constant REGN1945 (a negative hIgG4 isotype control), as assessed by Luciferase production. **Figure 2B** is a set of graphs depicting the activation of engineered reporter T-cells co-incubated with HEK293/hCD20, HEK293/hCD20/hCD22, or Raji/CD80 and CD86 negative cells in addition to 200pM constant REGN2281 (anti-CD20 x anti-CD3), as assessed by Luciferase production.

[0041] Figure 3A and 3B are a set of graphs depicting that anti-CD28/anti-CD22 bispecific antibodies increase IL-2 production in the presence of primary T-cell stimulation and CD22 target expression. More specifically, **Figure 3A** is a set of graphs depicting the activation of CD4⁺ T-cells co-incubated with HEK293/hCD20, HEK293/hCD20/hCD22, or Raji/CD80 and CD86 negative cells in the presence of 2nM constant REGN1945 (hIgG4 isotype control), as assessed by IL-2 production. **Figure 3B** is a set of graphs depicting the activation of CD4⁺ T-cells co-incubated with HEK293/hCD20, HEK293/hCD20/hCD22, or Raji/CD80 and CD86 negative cells in the presence of 2nM constant REGN2281 (anti-CD20 x anti-CD3), as assessed by IL-2 production.

[0042] Figure 4 is a set of graphs showing that a combination of REGN5837 with cemiplimab enhances IL-2 release above REGN5837 treatment alone in cells engineered to express PD-L1.

[0043] Figure 5A is a set of graphs showing that a combination of REGN5837 with cemiplimab enhances IL-2 release in the presence of NALM6 cells engineered to express PD-L1.

[0044] Figure 5B is a set of graphs showing that a combination of REGN5837 with cemiplimab enhances IL-2 release above REGN5837 treatment alone in RAJI cells engineered to express PD-L1.

CLAIMS

What is claimed is:

1. An isolated bispecific antigen binding molecule comprising:
 - a) a first antigen-binding domain (D1) that binds human CD28; and
 - b) a second antigen-binding domain (D2) that specifically binds human CD22 on a target tumor cell.
2. The isolated bispecific antigen binding molecule of claim 1, wherein the second antigen-binding domain (D2) binds an epitope on human CD22 comprising one or more amino acids of SEQ ID NO:57, SEQ ID NO:58, and/or SEQ ID NO:59.
3. The isolated bispecific antigen binding molecule of claim 1 or 2, wherein the bispecific antigen binding molecule binds human CD22 with a K_D of less than about 15 nM as measured by surface plasmon resonance at 25°C.
4. The isolated bispecific antigen binding molecule of one of claim 1-3, wherein the bispecific antigen binding molecule binds *Macaca fascicularis* CD22 with a K_D of less than about 60 μ M as measured by surface plasmon resonance at 25°C.
5. The isolated bispecific antigen binding molecule of any one of claims 1-4, wherein the bispecific antigen binding molecule binds human CD28 with a K_D of less than about 45 μ M as measured by surface plasmon resonance at 25°C.
6. The isolated bispecific antigen binding molecule of any one of claims 1-5, wherein the bispecific antigen binding molecule binds to the surface of cells expressing human CD28 with an EC_{50} of less than about 1×10^{-8} M as measured by an *in vitro* FACS binding assay.
7. The isolated bispecific antigen binding molecule of any one of claims 1-6, wherein the bispecific antigen binding molecule binds to the surface of cells expressing human CD22 with an EC_{50} of less than about 1×10^{-8} M as measured by an *in vitro* FACS binding assay.
8. The isolated bispecific antigen binding molecule of any one of claims 1-7, wherein the bispecific antigen binding molecule demonstrates a costimulatory effect when

used in conjunction with an anti-CD20xCD3 bispecific antibody.

9. The isolated bispecific antigen binding molecule of claim 8, wherein the costimulatory effect is one or more of the following: (activating T-cells, inducing IL-2 release, inducing CD25+ up-regulation in human PBMCs; and increasing human T-cell mediated cytotoxicity on CD22 expressing cell lines.

10. The isolated bispecific antigen binding molecule of any one of claims 1-9, wherein the first antigen-binding domain (D1) comprises:

a) three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid of SEQ ID NO: 26; and

b) three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:10.

11. The isolated bispecific antigen binding molecule of claim 10, comprising:

a) a HCDR1 comprising the amino acid sequence of SEQ ID NO: 28, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 30, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 32.

12. The isolated bispecific antigen-binding molecule of claim 12, comprising:

a) a LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

13. The isolated bispecific antigen-binding molecule of claim 10, wherein the first antigen-binding domain comprises:

a) a set of HCVR CDRs (HCDR1, HCDR2, HCDR3), the set comprising the amino acid sequences of SEQ ID NOs: 28, 30, and 32, and a set of LCVR CDRs (LCDR1, LCDR2, LCDR3), the set comprising the amino acid sequences of SEQ ID NOs: 12, 14, and 16.

14. The isolated bispecific antigen-binding molecule of claim 10, wherein the first antigen-binding domain comprises a HCVR/ LCVR pair comprising the amino acid sequences of SEQ ID NOs: 26/10.

15. The isolated bispecific antigen-binding molecule of any one of claims 1-14, wherein the second antigen-binding domain comprises:

- a) three HCDRs contained within a HCVR comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 2 and 18; and
- b) three LCDRs contained within a LCVR comprising the amino acid sequence of SEQ ID NO:10.

16. The isolated bispecific antigen binding molecule of claim 15, wherein the second antigen-binding domain comprises:

- a) a HCDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 4 and 20;
- b) a HCDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 6 and 22 and
- c) a HCDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 8 and 24.

17. The isolated bispecific antigen-binding molecule of claim 16, wherein the second antigen-binding domain comprises:

- a) a LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

18. The isolated bispecific antigen binding molecule of claim 17, wherein the second antigen-binding domain comprises:

- a) a set of HCVR CDRs (HCDR1, HCDR2, HCDR3), the set comprising amino acid sequences selected from the group consisting of SEQ ID NOs: 4, 6, 8; and 20, 22, 24; and a set of LCVR CDRs (LCDR1, LCDR2, LCDR3), the set comprising amino the acid sequences of SEQ ID NOs: 12, 14, 16.

19. The isolated bispecific antigen-binding molecule of any one of claims 1-18, comprising:

- a) a first antigen-binding domain that comprises HCVR CDRs comprising amino acid sequences of SEQ ID NOs: 28, 30, 32, and LCVR CDRs comprising amino acid sequences of SEQ ID NOs: 12, 14, 16; and
- b) a second antigen binding domain that comprises HCVR CDRs comprising amino acid sequences of SEQ ID NOs: 4, 6, 8, and LCVR CDRs comprising amino acid sequences of SEQ ID NOs: 12, 14, 16.

20. The isolated bispecific antigen-binding molecule of any one of claims 1-18, comprising:

a) a first antigen-binding domain that comprises HCDRs comprising amino acid sequences of SEQ ID NOs: 28, 30, 32, and LCDRs comprising amino acid sequences of SEQ ID NOs: 12, 14, 16; and

b) a second antigen binding domain that comprises HCDRs comprising amino acid sequences of SEQ ID NOs: 20, 22, 24, and LCDRs comprising amino acid sequences of SEQ ID NOs: 12, 14, 16.

21. The isolated bispecific antigen-binding molecule of any one of claims 1-18, comprising:

a) a first antigen binding domain that comprises a HCVR/ LCVR pair comprising amino acid sequences of SEQ ID NOs: 26/10; and

b) a second antigen binding domain that comprises a HCVR/ LCVR pair comprising amino acid sequences of SEQ ID NOs: 2/10.

22. The isolated bispecific antigen-binding molecule of any one of claims 1-18, wherein

a) the first antigen binding domain comprises a HCVR/LCVR pair comprising amino acid sequences of SEQ ID NOs: 26/10; and

b) the second antigen binding domain comprises a HCVR/LCVR pair comprising amino acid sequences of SEQ ID NOs: 18/10.

23. An isolated bispecific antigen binding molecule that competes for binding to CD22, or binds to the same epitope on CD22 as a reference antibody, wherein the reference antibody comprises a first antigen-binding domain having an HCVR/LCVR pair comprising the amino acid sequences of SEQ ID NOs: 26/10 and a second antigen-binding domain having an HCVR/LCVR pair comprising the amino acid sequences of SEQ ID NOs: 2/10 or 18/10.

24. An isolated bispecific antigen binding molecule that competes for binding to human CD28, or binds to the same epitope on human CD28 as a reference antibody, wherein the reference antibody comprises a first antigen-binding domain having an HCVR/LCVR pair comprising the amino acid sequences of SEQ ID NOs: 26/10 and a second antigen-binding domain having an HCVR/LCVR pair comprising the amino acid sequences of SEQ ID NOs: 2/10 or 18/10.

25. A pharmaceutical composition comprising the bispecific antigen-binding molecule of any one of claims 1 to 24, and a pharmaceutically acceptable carrier or diluent.

26. A nucleic acid molecule comprising a nucleotide sequence encoding a bispecific antibody of any one of claims 1 to 24.

27. An expression vector comprising the nucleic acid of claim 26.

28. A host cell comprising the expression vector of claim 27.

29. Use of an isolated bispecific antibody of any one of claims 1 to 24 or a pharmaceutical composition of claim 25 in the manufacture of a medicament for inhibiting a B-cell proliferative disorder in a subject, wherein said antibody or pharmaceutical composition is to be administered to the subject, thereby inhibiting growth of the B-cell lymphoma in the subject.

30. The use of claim 29, wherein a second therapeutic agent is to be further administered to the subject.

31. The use of claim 30, wherein the second therapeutic agent comprises an anti-tumor agent, radiotherapy, an antibody drug conjugate, a bispecific antibody conjugated to an anti-tumor agent, a checkpoint inhibitor, or combinations thereof.

32. Use of an isolated bispecific antibody of any one of claims 1 to 24 or a pharmaceutical composition of claim 25 in the manufacture of a medicament for treating a patient suffering from B-cell proliferative disorder, or from another CD22-expressing cell malignancy, wherein said antibody or pharmaceutical composition is to be administered to the subject, thereby treating the patient suffering from a B-cell lymphoma or from another CD-22 expressing cell malignancy.

33. The use of claims 32, wherein a second therapeutic agent is to be further administered to the subject.

34. The use of claim 33, wherein the second therapeutic agent comprises an anti-tumor agent, radiotherapy, an antibody drug conjugate, a bispecific antibody conjugated with

an anti-tumor agent, a checkpoint inhibitor, or combinations thereof.

35. The use of either one of claims 31 or 34, wherein the second therapeutic agent is a different bispecific antibody comprising a first antigen binding domain that binds to the same tumor target antigen and a second antigen binding domain that binds to CD3 on T cells.