specific binding to a second target cell antigen. In some examples, the first target antigen is an activating T cell antigen, such as CD3, and/or the second target cell antigen is a tumor antigen (e.g., HER2).

In one aspect, the present disclosure refers to a bispecific antigen-binding molecule comprising a monovalent arm and a bivalent arm, wherein:

(a) the monovalent arm comprises a first antigen-binding moiety, wherein the C-terminus of the first antigen-binding moiety is fused to the N-terminus of a first Fc subunit;

(b) the bivalent arm comprises a second antigen-binding moiety and a third antigen-binding moiety, wherein the C-terminus of the third antigen-binding moiety is fused to the N-terminus of the second antigen-binding moiety, and the C-terminus of the second antigen-binding moiety is fused to an N-terminus of a second Fc subunit; and

(c) the first Fc subunit is associated with the second Fc subunit to form an Fc domain,

wherein the first antigen-binding moiety is capable of specific binding to CD3, and the second antigen-binding moiety and the third antigen-binding moiety are each capable of specific binding to HER2, wherein the monovalent binding affinity (K_D) of the first antigen-binding moiety is from 10 nM to 100 nM as measured by surface plasmon resonance, and wherein the monovalent K_D of each of the second antigen-binding moiety and the third antigen-binding moiety is from 20 nM to 50 nM as measured by surface plasmon resonance.

In some examples, the tumor antigen is expressed on (a) a tumor cell in a subject and (b) at least one type of non-tumor cell in the subject.

In some examples, the ratio of tumor antigen copy number on the non-tumor cells to the tumor cells is from 1:10 to 1:1,000 (e.g., from 1:100 to 1:200). In some examples, the tumor antigen copy number is from 10^2 to 10^5 on a non-tumor cell and from 10^3 to 10^7 on a tumor cell.

In some examples, the tumor antigen copy number (e.g., average tumor antigen copy number, e.g., HER2 copy number, e.g., average HER2 copy number) on the tumor cells (e.g., HER2-positive tumor cells) is greater than 10^5 per cell (e.g., from 10^5 to 10^7 per cell, or from 10^5 to 10^6 per cell). In some examples, the tumor antigen copy number (e.g., average tumor antigen copy number, e.g., HER2 copy number, e.g., average HER2 copy number) is ≥ 200,000 per tumor cell (e.g., HER2-positive tumor cell). In some examples, the tumor antigen copy number (e.g., average tumor antigen copy number, e.g., HER2 copy number, e.g., average HER2 copy number) is ≤ 200,000 per non-tumor cell (e.g., non-cancerous cell, e.g., healthy cell).

In some examples, the monovalent binding affinity (K_D) of the second antigen-binding moiety and/or the third antigen-binding moiety is from 10 nM to 100 nM (e.g., from 20 nM to 90 nM, from 30 nM to 80 nM, from 40 nM to 60 nM, e.g., from 25 nM to 55 nM). In one example, the monovalent binding affinity (K_D) of the second antigen-binding moiety and/or the third antigen-binding moiety is from 20 nM to 50 nM. In one example, the monovalent binding affinity (K_D) of the second antigen-binding moiety and the third antigen-binding moiety is from 20 nM to 50 nM.

In some examples, the monovalent K_D of the second antigen-binding moiety is the K_D of the second antigen-binding moiety in Fab format measured using surface plasmon resonance (e.g., BIACORE® surface plasmon resonance) and wherein the monovalent K_D of the third antigen-binding moiety is the K_D of the third antigen-binding moiety in Fab format measured using surface plasmon resonance (e.g., BIACORE® surface plasmon resonance).

In some examples, the monovalent dissociation rate of the second antigen-binding moiety and/or the third antigen-binding moiety is from 10^{-3}/second to 10^{-1}/second (e.g., from 10^{-2}/second to 30^{-2}/second). In some examples, the monovalent K_D of the first antigen-binding moiety is from 10 nM to 100 nM (e.g., from 20 nM to 90 nM, from 20 nM to 80 nM, from 30 nM to 70 nM, or from 40 nM to 60 nM).

In any of the preceding examples, the first antigen-binding moiety may be a Fab molecule (Fab_A) comprising a variable heavy chain (VH_A) region and a variable light chain (VL_A) region; the second antigen-binding moiety is a Fab molecule (Fab_{B1}) comprising a variable heavy chain (VH_{B1}) region and a variable light chain (VL_{B1}) region; and/or the third antigen-binding moiety is a Fab molecule (Fab_{B2}) comprising a variable heavy chain (VH_{B2}) region and a variable light chain (VL_{B2}) region. Thus, in some examples, the first antigen-binding moiety is a Fab_A comprising a VH_A region and a VL_A region, the second antigen-binding moiety is a Fab_{B1} comprising a VH_{B1} region and a VL_{B1} region, and third antigen-binding moiety is a Fab_{B2} comprising a VH_{B2} region and a VL_{B2} region.

WHAT IS CLAIMED IS:

1. A bispecific antigen-binding molecule comprising a monovalent arm and a bivalent arm, wherein:

(a) the monovalent arm comprises a first antigen-binding moiety, wherein the C-terminus of the first antigen-binding moiety is fused to the N-terminus of a first Fc subunit;

(b) the bivalent arm comprises a second antigen-binding moiety and a third antigen-binding moiety, wherein the C-terminus of the third antigen-binding moiety is fused to the N-terminus of the second antigen-binding moiety, and the C-terminus of the second antigen-binding moiety is fused to an N-terminus of a second Fc subunit; and

(c) the first Fc subunit is associated with the second Fc subunit to form an Fc domain,

wherein the first antigen-binding moiety is capable of specific binding to CD3, and the second antigen-binding moiety and the third antigen-binding moiety are each capable of specific binding to HER2, wherein the monovalent binding affinity (K_D) of the first antigen-binding moiety is from 10 nM to 100 nM as measured by surface plasmon resonance, and wherein the monovalent K_D of each of the second antigen-binding moiety and the third antigen-binding moiety is from 20 nM to 50 nM as measured by surface plasmon resonance.

2. The bispecific antigen binding molecule of claim 1, wherein the second and third antigen-binding moieties bind domain IV of HER2;

wherein optionally the monovalent dissociation rate of the second antigen-binding moiety and/or the third antigen-binding moiety is from 10^{-3}/second to 10^{-1}/second,

wherein optionally the monovalent dissociation rate of each of the second antigen-binding moiety and the third antigen-binding moiety is from 10^{-2}/second to 30^{-2}/second;

wherein optionally the monovalent K_D of the first antigen-binding moiety is from 20 nM to 80 nM as measured by surface plasmon resonance,

wherein optionally the monovalent K_D of the first antigen-binding moiety is from 40 nM to 60 nM as measured by surface plasmon resonance.

3. The bispecific antigen-binding molecule of claim 1 or 2, wherein the first antigen-binding moiety is a Fab molecule (Fab_A) comprising a variable heavy chain (VH_A) region and a variable light chain (VL_A) region.

4. The bispecific antigen-binding molecule of any one of claims 1-3, wherein the second antigen-binding moiety is a Fab molecule (Fab_{B1}) comprising a variable heavy chain (VH_{B1}) region and a variable light chain (VL_{B1}) region and/or the third antigen-binding moiety is a Fab molecule (Fab_{B2}) comprising a variable heavy chain (VH_{B2}) region and a variable light chain (VL_{B2}) region;

wherein optionally the first antigen-binding moiety is a Fab_A comprising a VH_A region and a VL_A region, the second antigen-binding moiety is a Fab_{B1} comprising a VH_{B1} region and a VL_{B1} region, and the third antigen-binding moiety is a Fab_{B2} comprising a VH_{B2} region and a VL_{B2} region;

wherein optionally (a) the VH_{B1} and the VH_{B2} share at least 95% sequence identity; (b) the VL_{B1} and the VL_{B2} share at least 95% sequence identity; or (c) the VH_{B1} and the VH_{B2} share at least 95% sequence identity and the VL_{B1} and the VL_{B2} share at least 95% sequence identity;

wherein optionally the VH_{B1} region and/or the VH_{B2} region comprises an amino acid substitution at one, two, three, or all four residues of N54, D98, F100, and/or Y102, according to the Kabat numbering system,

wherein optionally the VH_{B1} region and/or the VH_{B2} region comprises one, two, three, or all four of the following amino acid substitutions: N54E, D98A, D98T, F100A, and/or Y102V, according to the Kabat numbering system;

wherein optionally the VL_{B1} region and/or the VL_{B2} region comprises an amino acid substitution at one, two, or all three residues of N30, Y55, and/or H91, according to the Kabat numbering system,

wherein optionally the VL_{B1} region and/or the VL_{B2} region comprises one, two, or all three of the following amino acid substitutions: N30S, Y55E, and/or H91A.

5. The bispecific antigen-binding molecule of claim 4, wherein the VH_{B1} region comprises one, two, or all three of the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 19, and/or

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 20;

wherein optionally the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 24,

wherein optionally the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 24;

wherein optionally the VL_{B1} region comprises one, two, or all three of the following HVRs:

(a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(b) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 22, and/or

(c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26;

wherein optionally the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 27,

wherein optionally the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 27;

wherein optionally the VH_{B1} comprises the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 19, and

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 20;

and the VL_{B1} comprises the following HVRs:

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 22, and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26;

wherein optionally the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 24, and the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 27,

wherein optionally the VH_{B1} region comprises the amino acid of SEQ ID NO: 24, and the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 27;

wherein optionally the VH_{B2} region comprises one, two, or all three of the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 19, or

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 20;

wherein optionally the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 24,

wherein optionally the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 24;

wherein optionally the VL_{B2} region comprises one, two, or all three of the following HVRs:

(a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(b) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 22, and/or

(c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26;

wherein optionally the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 27,

wherein optionally the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 27;

wherein optionally the VH_{B2} comprises the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 19, and

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 20;

and the VL_{B2} comprises the following HVRs:

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 22, and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26;

wherein optionally the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 24, and the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 27,

wherein optionally the VH_{B2} region comprises the amino acid of SEQ ID NO: 24, and the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 27;

wherein optionally the VL_{B1} region and/or the VL_{B2} region comprises one or more liability fixed residues,

wherein optionally the one or more liability fixed residues comprises the amino acid substitution of N30S;

wherein optionally the VH_{B1} region and/or the VH_{B2} region comprises one or more liability fixed residues,

wherein optionally the one or more liability fixed residues comprises one or more amino acid substitutions selected from the group consisting of N54E, D98A, and D98T.

6. The bispecific antigen-binding molecule of claim 4, wherein the VH_{B1} region comprises one, two, or all three of the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 19, and/or

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 32;

wherein optionally the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 33,

wherein optionally the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 33;

wherein optionally the VL_{B1} region comprises one, two, or all three of the following HVRs:

(a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(b) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 22, or

(c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 23;

wherein optionally the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 25,

wherein optionally the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 25;

wherein optionally the VH_{B1} comprises the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 19, and

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 32;

and the VL_{B1} comprises the following HVRs:

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 22, and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 23;

wherein optionally the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 33; and the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 25,

wherein optionally the VH_{B1} region comprises the amino acid of SEQ ID NO: 33, and the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 25;

wherein optionally the VH_{B2} region comprises one, two, or all three of the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 19, and/or

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 32;

wherein optionally the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 33,

wherein optionally the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 33;

wherein optionally the VL_{B2} region comprises one, two, or all three of the following HVRs:

(a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(b) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 22, and/or

(c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 23;

wherein optionally the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 25,

wherein optionally the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 25;

wherein optionally the VH_{B2} comprises the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 19, and

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 32;

and the VL_{B2} comprises the following HVRs:

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 22, and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 23;

wherein optionally the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 33, and the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 25,

wherein optionally the VH_{B2} region comprises the amino acid of SEQ ID NO: 33, and the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 25.

7. The bispecific antigen-binding molecule of claim 4, wherein the VH_{B1} region comprises one, two, or all three of the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36, and/or

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 43;

wherein optionally the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 44,

wherein optionally the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 44;

wherein optionally the VL_{B1} region comprises one, two, or all three of the following HVRs:

(a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(b) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and/or

(c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26;

wherein optionally the VL region of the second antigen-binding moiety comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 48,

wherein optionally the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 48;

wherein optionally the VH_{B1} comprises the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36, and

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 43;

and the VL_{B1} comprises the following HVRs:

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26;

wherein optionally the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 44, and the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 48,

wherein optionally the VH_{B1} region comprises the amino acid of SEQ ID NO: 44, and the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 48;

wherein optionally the VH_{B2} region comprises one, two, or all three of the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36, and/or

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 43;

wherein optionally the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 44,

wherein optionally the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 44;

wherein optionally the VL_{B2} region comprises one, two, or all three of the following HVRs:

(a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(b) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and/or

(c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26;

wherein optionally the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 48,

wherein optionally the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 48;

wherein optionally the VH_{B2} comprises the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36, and

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 43;

and the VL_{B2} comprises the following HVRs:

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26;

wherein optionally the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 44, and the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 48,

wherein optionally the VH_{B2} region comprises the amino acid of SEQ ID NO: 44, and the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 48.

8. The bispecific antigen-binding molecule of claim 4, wherein the VH_{B1} region comprises one, two, or all three of the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36, and/or

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 37;

wherein optionally the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 41,

wherein optionally the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 41;

wherein optionally the VL_{B1} region comprises one, two, or all three of the following HVRs:

(a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38,

(b) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and/or

(c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26;

wherein optionally the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 49,

wherein optionally the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 49;

wherein optionally the VH_{B1} comprises the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36, and

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 37;

and the VL_{B1} comprises the following HVRs:

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38,

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26;

wherein optionally the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 41, and the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 49,

wherein optionally the VH_{B1} region comprises the amino acid of SEQ ID NO: 41, and the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 49;

wherein optionally the VH_{B2} region comprises one, two, or all three of the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36, and/or

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 37;

wherein optionally the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 41,

wherein optionally the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 41;

wherein optionally the VL_{B2} region comprises one, two, or all three of the following HVRs:

(a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38,

(b) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and/or

(c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26;

wherein optionally the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 49,

wherein optionally the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 49;

wherein optionally the VH_{B2} comprises the following HVRs:

(a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(b) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36, and

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 37;

and the VL_{B2} comprises the following HVRs:

(d) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38,

(e) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and

(f) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26;

wherein optionally the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 41, and the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 49,

wherein optionally the VH_{B2} region comprises the amino acid of SEQ ID NO: 41, and the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 49.

9. The bispecific antigen-binding molecule of any one of claims 3-8, wherein the VH_A region comprises one, two, or all three of the following 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, and/or

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 3;

wherein optionally the VH_A region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 7,

wherein optionally the VH_A region comprises the amino acid sequence of SEQ ID NO: 7;

wherein optionally the VL_A region comprises one, two, or all three of the following HVRs:

(a) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 4,

(b) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 5, and/or

(c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 6;

wherein optionally the VL_A region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 8,

wherein optionally the VL_A region comprises the amino acid sequence of SEQ ID NO: 8;

wherein optionally the VH_A comprises the following 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, and

(c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 3;

and the VL_A comprises the following HVRs:

(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;

wherein optionally the VH_A region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 7, and the VL_A region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 8,

wherein optionally the VH_A region comprises the amino acid of SEQ ID NO: 7, and the VL_A region comprises the amino acid sequence of SEQ ID NO: 8.

10. A bispecific antigen-binding molecule comprising a monovalent arm and a bivalent arm, wherein:

(a) the monovalent arm comprises a Fab_A, wherein the C-terminus of the Fab_A is fused to an N-terminus of a first Fc subunit, and wherein the Fab_A comprises the following HVRs:

(i) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 1,

(ii) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 2,

(iii) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 3,

(iv) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 4,

(v) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 5, and

(vi) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 6;

(b) the bivalent arm comprises a Fab_{B1} and a Fab_{B2}, wherein the C-terminus of the Fab_{B2} is fused to the N-terminus of the Fab_{B1}, and the C-terminus of the Fab_{B1} is fused to an N-terminus of a second Fc subunit, wherein the Fab_{B1} and the Fab_{B2} each comprise the following HVRs:

(i) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(ii) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 19,

(iii) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 20,

(iv) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(v) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 22, and

(vi) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26; and

(c) the first Fc subunit is associated with the second Fc subunit to form an Fc domain.

11. The bispecific antigen-binding molecule of claim 10, wherein:

(a) the Fab_A comprises a VH_A region and a VL_A region, wherein the VH_A region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 7, and the VL_A region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 8;

(b) the Fab_{B1} comprises a VH_{B1} region and a VL_{B1} region, wherein the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 24, and the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 27; and

(c) the Fab_{B2} comprises a VH_{B2} region and a VL_{B2} region, wherein the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 24, and the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 27,

wherein optionally:

(a) the VH_A region comprises the amino acid sequence of SEQ ID NO: 7, and the VL_A region comprises the amino acid sequence of SEQ ID NO: 8;

(b) the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 24, and the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 27; and

(c) the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 24, and the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 27.

12. A bispecific antigen-binding molecule comprising a monovalent arm and a bivalent arm, wherein:

(a) the monovalent arm comprises a Fab_A, wherein the C-terminus of the Fab_A is fused to an N-terminus of a first Fc subunit, and wherein the Fab_A comprises the following HVRs:

(i) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 1,

(ii) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 2,

(iii) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 3,

(iv) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 4,

(v) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 5, and

(vi) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 6;

(b) the bivalent arm comprises a Fab_{B1} and a Fab_{B2}, wherein the C-terminus of the Fab_{B2} is fused to the N-terminus of the Fab_{B1}, and the C-terminus of the Fab_{B1} is fused to an N-terminus of a second Fc subunit, wherein the Fab_{B1} and the Fab_{B2} each comprise the following HVRs:

(i) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(ii) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 19,

(iii) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 32,

(iv) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(v) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 22, and

(vi) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 23; and

(c) the first Fc subunit is associated with the second Fc subunit to form an Fc domain.

13. The bispecific antigen-binding molecule of claim 12, wherein:

(a) the Fab_A comprises a VH_A region and a VL_A region, wherein the VH_A region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 7, and the VL_A region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 8;

(b) the Fab_{B1} comprises a VH_{B1} region and a VL_{B1} region, wherein the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 33, and the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 25; and

(c) the Fab_{B2} comprises a VH_{B2} region and a VL_{B2} region, wherein the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 33, and the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 25,

wherein optionally:

(a) the VH_A region comprises the amino acid sequence of SEQ ID NO: 7, and the VL_A region comprises the amino acid sequence of SEQ ID NO: 8;

(b) the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 33, and the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 25; and

(c) the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 33, and the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 25.

14. A bispecific antigen-binding molecule comprising a monovalent arm and a bivalent arm, wherein:

(a) the monovalent arm comprises a Fab_A, wherein the C-terminus of the Fab_A is fused to an N-terminus of a first Fc subunit, and wherein the Fab_A comprises the following HVRs:

(i) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 1,

(ii) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 2,

(iii) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 3,

(iv) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 4,

(v) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 5, and

(vi) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 6;

(b) the bivalent arm comprises a Fab_{B1} and a Fab_{B2}, wherein the C-terminus of the Fab_{B2} is fused to the N-terminus of the Fab_{B1}, and the C-terminus of the Fab_{B1} is fused to an N-terminus of a second Fc subunit, wherein the Fab_{B1} and the Fab_{B2} each comprise the following HVRs:

(i) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(ii) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36,

(iii) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 43,

(iv) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(v) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and

(vi) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26; and

(c) the first Fc subunit is associated with the second Fc subunit to form an Fc domain.

15. The bispecific antigen-binding molecule of claim 14, wherein:

(a) the Fab_A comprises a VH_A region and a VL_A region, wherein the VH_A region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 7, and the VL_A region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 8;

(b) the Fab_{B1} comprises a VH_{B1} region and a VL_{B1} region, wherein the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 44, and the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 48; and

(c) the Fab_{B2} comprises a VH_{B2} region and a VL_{B2} region, wherein the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 44, and the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 48,

wherein optionally:

(a) the VH_A region comprises the amino acid sequence of SEQ ID NO: 7, and the VL_A region comprises the amino acid sequence of SEQ ID NO: 8;

(b) the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 44, and the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 48; and

(c) the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 44, and the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 48.

16. A bispecific antigen-binding molecule comprising a monovalent arm and a bivalent arm, wherein:

(a) the monovalent arm comprises a Fab_A, wherein the C-terminus of the Fab_A is fused to an N-terminus of a first Fc subunit, and wherein the Fab_A comprises the following HVRs:

(i) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 1,

(ii) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 2,

(iii) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 3,

(iv) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 4,

(v) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 5, and

(vi) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 6;

(b) the bivalent arm comprises a Fab_{B1} and a Fab_{B2}, wherein the C-terminus of the Fab_{B2} is fused to the N-terminus of the Fab_{B1}, and the C-terminus of the Fab_{B1} is fused to an N-terminus of a second Fc subunit, wherein the Fab_{B1} and the Fab_{B2} each comprise the following HVRs:

(i) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(ii) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36,

(iii) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 37,

(iv) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38,

(v) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and

(vi) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26; and

(c) the first Fc subunit is associated with the second Fc subunit to form an Fc domain.

17. The bispecific antigen-binding molecule of claim 16, wherein:

(a) the Fab_A comprises a VH_A region and a VL_A region, wherein the VH_A region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 7, and the VL_A region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 8;

(b) the Fab_{B1} comprises a VH_{B1} region and a VL_{B1} region, wherein the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 41, and the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 49; and

(c) the Fab_{B2} comprises a VH_{B2} region and a VL_{B2} region, wherein the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 41, and the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 49,

wherein optionally:

(a) the VH_A region comprises the amino acid sequence of SEQ ID NO: 7, and the VL_A region comprises the amino acid sequence of SEQ ID NO: 8;

(b) the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 41, and the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 49; and

(c) the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 41, and the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 49.

18. The bispecific antigen-binding molecule of any one of claims 1-17, wherein the Fc domain is an IgG Fc domain,

wherein optionally the IgG Fc domain is an IgG_1 or IgG_4 Fc domain;

wherein optionally the Fc domain is a human Fc domain.

19. The bispecific antigen-binding molecule of any one of claims 1-18, wherein the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor and/or effector function,

wherein optionally the one or more amino acid substitutions that reduces binding to an Fc receptor and/or effector function is at N297,

wherein optionally the first Fc subunit and the second Fc subunit each comprise the amino acid substitution of N297G;

wherein optionally the Fc receptor is an Fcγ receptor;

wherein optionally the effector function is antibody-dependent cell-mediated cytotoxicity (ADCC).

20. The bispecific antigen-binding molecule of any one of claims 1-19, wherein the Fc domain comprises a modification configured to promote the association of the first Fc subunit with the second Fc subunit,

wherein optionally an amino acid residue in the CH3 domain of the second Fc subunit is replaced with an amino acid residue having a larger side chain volume, thereby generating a protuberance within the CH3 domain of the second Fc subunit which is positionable in a cavity within the CH3 domain of the first Fc subunit, and an amino acid residue in the CH3 domain of the first Fc subunit is replaced with an amino acid residue having a smaller side chain volume, thereby generating a cavity within the CH3 domain of the first Fc subunit within which the protuberance within the CH3 domain of the second Fc subunit is positionable,

wherein optionally the CH3 domain of the second Fc subunit comprises the amino acid substitution of T366, and the CH3 domain of the first Fc subunit comprises amino acid substitutions at one, two, or all three of T366, L368, and/or Y407,

wherein optionally the CH3 domain of the second Fc subunit comprises the amino acid substitution of T366W, and the CH3 domain of the first Fc subunit comprises one, two, or all three amino acid substitutions of T366S, L368A, and/or Y407V.

21. The bispecific antigen-binding molecule of any one of claims 1-20, wherein the C-terminus of the third antigen-binding moiety is fused to the N-terminus of the second antigen-binding moiety via a peptide linker,

wherein optionally the peptide linker is from 5 to 20 amino acids in length,

wherein optionally the peptide linker comprises the amino acid sequence of SEQ ID NO: 50,

wherein optionally the antigen-binding molecule comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 53,

wherein optionally the peptide linker comprises the amino acid sequence of SEQ ID NO: 51,

wherein optionally the antigen-binding molecule comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 56.

22. An isolated nucleic acid encoding the bispecific antigen-binding molecule of any one of claims 1-21.

23. A vector comprising the isolated nucleic acid of claim 22.

24. A host cell comprising the isolated nucleic acid of claim 22 or the vector of claim 23.

25. The host cell of claim 24, wherein the host cell is a mammalian cell,
wherein optionally the mammalian cell is a Chinese hamster ovary (CHO) cell.

26. The host cell of claim 24, wherein the host cell is a prokaryotic cell,
wherein optionally the prokaryotic cell is an *E. coli* cell.

27. A method of producing the bispecific antigen-binding molecule of any one of claims 1-21, the method comprising culturing the host cell of any one of claims 24-26 in a culture medium.

28. The method of claim 27, wherein the method further comprises recovering the bispecific antigen-binding molecule from the host cell or the culture medium.

29. A set of isolated nucleic acids encoding the bispecific antigen-binding molecule of any one of claims 1-21.

30. A set of vectors, wherein each vector of the set comprises an isolated nucleic acid of the set of isolated nucleic acids of claim 29.

31. A set of host cells, wherein each host cell of the set comprises an isolated nucleic acid of the set of isolated nucleic acids of claim 29 or a vector of the set of vectors of claim 30.

32. The set of host cells of claim 31, wherein the host cells comprise mammalian cells,
wherein optionally the mammalian cells are CHO cells.

33. The set of host cells of claim 31, wherein the host cells comprise prokaryotic cells,
wherein optionally the prokaryotic cells are *E. coli* cells.

34. A method of producing the bispecific antigen-binding molecule of any one of claims 1-21, the method comprising culturing the set of host cells of any one of claims 31-33 in culture medium.

35. The method of claim 34, wherein the method further comprises recovering the bispecific antigen-binding molecule from the set of host cells or the culture medium.

36. An immunoconjugate comprising the bispecific antigen-binding molecule of any one of claims 1-21 and a cytotoxic agent.

37. A composition comprising the bispecific antigen-binding molecule of any one of claims 1-21.

38. The composition of claim 37, further comprising a pharmaceutically acceptable carrier, excipient, or diluent;

wherein optionally the composition is a pharmaceutical composition;

wherein optionally the composition further comprises a PD-1 axis binding antagonist or an additional therapeutic agent.

39. The bispecific antigen-binding molecule of any one of claims 1-21 for use as a medicament.

40. The bispecific antigen-binding molecule of any one of claims 1-21 for use (a) in treating or delaying progression of a HER2-positive cancer in a subject in need thereof, or (b) in enhancing immune function in a subject having a HER2-positive cancer.

41. The bispecific antigen-binding molecule for use of claim 40, wherein the HER2-positive cancer is selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, non-small cell lung cancer, renal cancer, bladder cancer, pancreatic cancer, prostate cancer, liver cancer, head and neck cancer, melanoma, ovarian cancer, mesothelioma, glioblastoma, endometrial cancer, and osteosarcoma;

wherein optionally the HER2-positive cancer is characterized by tumor cells that express HER2 at an average copy number of 200,000 or more copies per cell.

42. Use of the bispecific antigen-binding molecule of any one of claims 1-21 in manufacture of a medicament for (a) treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, or (b) enhancing immune function in a subject having a HER2-positive cancer.

43. The use of claim 42, wherein the HER2-positive cancer is selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, non-small cell lung cancer, renal cancer, bladder cancer, pancreatic cancer, prostate cancer, liver cancer, head and neck cancer, melanoma, ovarian cancer, mesothelioma, glioblastoma, endometrial cancer, and osteosarcoma, wherein optionally the HER2-positive cancer is characterized by tumor cells that express HER2 at an average copy of 200,000 or more copies per cell.

44. The use of claim 42 or 43, wherein the bispecific antigen-binding molecule is formulated for administration to the subject at a dosage of about 0.01 mg/kg to about 10 mg/kg,

wherein optionally the bispecific antigen-binding molecule is formulated for administration to the subject at a dosage of about 0.1 mg/kg to about 10 mg/kg,

wherein optionally the bispecific antigen-binding molecule is formulated for administration to the subject at a dosage of about 1 mg/kg.

45. The use of any one of claims 42-44, wherein the medicament further comprises a PD-1 axis binding antagonist and/or an additional therapeutic agent,

wherein optionally (i) the PD-1 axis binding antagonist or additional therapeutic agent is formulated for administration prior to or subsequent to the administration of the bispecific antigen-binding molecule, or (ii) the PD-1 axis binding antagonist or additional therapeutic agent is formulated for concurrent administration with the bispecific antigen-binding molecule.

46. The use of claim 45, wherein the PD-1 axis binding antagonist is selected from the group consisting of a PD-L1 binding antagonist, a PD-1 binding antagonist, and a PD-L2 binding antagonist.

47. The use of claim 46, wherein the PD-1 axis binding antagonist is:

(i) a PD-L1 binding antagonist, wherein optionally the PD-L1 binding antagonist is selected from the group consisting of MPDL3280A (atezolizumab), MDX-1105, MEDI4736 (durvalumab), and MSB0010718C (avelumab);

(ii) a PD-1 binding antagonist, wherein optionally the PD-1 binding antagonist is selected from the group consisting of MDX-1106 (nivolumab), MK-3475 (pembrolizumab), MEDI-0680 (AMP-514), PDR001 (spartalizumab), REGN2810 (cemiplimab), and BGB-108; or

(iii) a PD-L2 binding antagonist, wherein optionally the PD-L2 binding antagonist is an antibody or an immunoadhesin.

48. The use of any one of claims 42-47, wherein the bispecific antigen-binding molecule is formulated for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally,

wherein optionally the bispecific antigen-binding molecule is formulated for administration subcutaneously, or intravenously.

49. The use of any one of claims 42-48, wherein the subject is a human.

50. A kit comprising:

(a) the composition of claim 37 or 38; and

(b) a package insert comprising instructions for use of the composition to treat or delay progression of a HER2-positive cancer.

51. The kit of claim 50, wherein the HER2-positive cancer is characterized by tumor cells that express HER2 at an average copy number of 200,000 or more copies per cell.

52. A bispecific antigen-binding molecule comprising a monovalent arm and a bivalent arm, wherein:

(a) the monovalent arm comprises a first antigen-binding moiety, wherein the C-terminus of the first antigen-binding moiety is fused to the N-terminus of a first Fc subunit;

(b) the bivalent arm comprises a second antigen-binding moiety and a third antigen-binding moiety, wherein the C-terminus of the third antigen-binding moiety is fused to the N-terminus

of the second antigen-binding moiety, and the C-terminus of the second antigen-binding moiety is fused to an N-terminus of a second Fc subunit; and

(c) the first Fc subunit is associated with the second Fc subunit to form an Fc domain,

wherein the first antigen-binding moiety is capable of specific binding to CD3, and the second antigen-binding moiety and the third antigen-binding moiety are each capable of specific binding to HER2, wherein the monovalent binding affinity (K_D) of the first antigen-binding moiety is from 10 nM to 100 nM as measured by surface plasmon resonance, wherein the monovalent K_D of each of the second antigen-binding moiety and the third antigen-binding moiety is from 20 nM to 50 nM as measured by surface plasmon resonance, and wherein:

(I) the first antigen-binding moiety comprises the following hypervariable regions (HVRs):

(i) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 1,

(ii) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 2,

(iii) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 3,

(iv) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 4,

(v) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 5, and

(vi) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 6; and

(II) the second antigen-binding moiety and the third antigen-binding moiety each comprise the following HVRs:

(i) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(ii) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36,

(iii) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 37,

(iv) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38,

(v) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and

(vi) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26.

53. The bispecific antigen-binding molecule of claim 52, wherein:

(a) the VH_A region comprises the amino acid sequence of SEQ ID NO: 7, and the VL_A region comprises the amino acid sequence of SEQ ID NO: 8;

(b) the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 41, and the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 49; and

(c) the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 41, and the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 49.

54. A bispecific antigen-binding molecule comprising a monovalent arm and a bivalent arm, wherein:

(a) the monovalent arm comprises a first antigen-binding moiety, wherein the C-terminus of the first antigen-binding moiety is fused to the N-terminus of a first Fc subunit;

(b) the bivalent arm comprises a second antigen-binding moiety and a third antigen-binding moiety, wherein the C-terminus of the third antigen-binding moiety is fused to the N-terminus of the second antigen-binding moiety, and the C-terminus of the second antigen-binding moiety is fused to an N-terminus of a second Fc subunit; and

(c) the first Fc subunit is associated with the second Fc subunit to form an Fc domain,

wherein the first antigen-binding moiety is capable of specific binding to CD3, and the second antigen-binding moiety and the third antigen-binding moiety are each capable of specific binding to HER2, wherein the monovalent binding affinity (K_D) of the first antigen-binding moiety is from 10 nM to 100 nM as measured by surface plasmon resonance, wherein the monovalent K_D of each of the second antigen-binding moiety and the third antigen-binding moiety is from 20 nM to 50 nM as measured by surface plasmon resonance, and wherein:

(I) the first antigen-binding moiety comprises the following hypervariable regions (HVRs):

(i) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 1,

(ii) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 2,

(iii) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 3,

(iv) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 4,

(v) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 5, and

(vi) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 6; and

(II) the second antigen-binding moiety and the third antigen-binding moiety each comprise the following HVRs:

(i) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 11,

(ii) an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 19,

(iii) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 20,

(iv) an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21,

(v) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 22, and

(vi) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26.

55. The bispecific antigen-binding molecule of claim 54, wherein:

(a) the VH_A region comprises the amino acid sequence of SEQ ID NO: 7, and the VL_A region comprises the amino acid sequence of SEQ ID NO: 8;

(b) the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 24, and the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 27; and

(c) the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 24, and the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 27.