

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.
2. The bispecific antigen binding molecule of claim 1, wherein the second and third antigen-binding moieties bind domain IV of HER2.
3. The bispecific antigen-binding molecule of claim 1 or 2, wherein the monovalent binding affinity (K_D) of each of the second antigen-binding moiety and the third antigen-binding moiety is from 10 nM to 100 nM.
4. The bispecific antigen-binding molecule of claim 3, 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.
5. The bispecific antigen-binding molecule of any one of claims 1-4, wherein 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.
6. The bispecific antigen-binding molecule of claim 5, wherein 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.
7. The bispecific antigen-binding molecule of any one of claims 1-6, wherein the monovalent K_D of the first antigen-binding moiety is from 10 nM to 100 nM.
8. The bispecific antigen-binding molecule of claim 7, wherein the monovalent K_D of the first antigen-binding moiety is from 20 nM to 80 nM.
9. The bispecific antigen-binding molecule of claim 8, wherein the monovalent K_D of the first antigen-binding moiety is from 40 nM to 60 nM.

10. The bispecific antigen-binding molecule of any of claims 1-9, wherein 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, 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.

11. The bispecific antigen-binding molecule of any one of claims 1-10, 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.

12. The bispecific antigen-binding molecule of any one of claims 1-11, 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.

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

14. The bispecific antigen-binding molecule of any one of claims 12-13, wherein (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.

15. The bispecific antigen-binding molecule of any one of claims 12-14, wherein 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.

16. The bispecific antigen-binding molecule of claim 15, wherein the VH_{B1} region and/or the VH_{B2} region comprises an amino acid substitution at one, two, three, four, or all five of the following residues: N54E, D98A, D98T, F100A, and/or Y102V, according to the Kabat numbering system.

17. The bispecific antigen-binding molecule of any one of claims 12-15, wherein 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.

18. The bispecific antigen-binding molecule of claim 17, wherein the VL_{B1} region and/or the VL_{B2} region comprises an amino acid substitution at one, two, or all three of the following residues: N30S, Y55E, and/or H91A.

19. The bispecific antigen-binding molecule of any one of claims 12-18, 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, or
- (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 20.

20. The bispecific antigen-binding molecule of any one of claims 12-19, wherein the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 24.

21. The bispecific antigen-binding molecule of claim 20, wherein the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 24.

22. The bispecific antigen-binding molecule of any one of claims 12-21, wherein 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: 26.

23. The bispecific antigen-binding molecule of any one of claims 12-22, wherein the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 27.

24. The bispecific antigen-binding molecule of claim 23, wherein the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 27.

25. The bispecific antigen-binding molecule of any one of claims 12-24, wherein 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.

26. The bispecific antigen-binding molecule of any one of claims 12-25, 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.

27. The bispecific antigen-binding molecule of claim 26, wherein 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.

28. The bispecific antigen-binding molecule of any one of claims 12-27, wherein 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.

29. The bispecific antigen-binding molecule of any one of claims 12-28, wherein the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 24.

30. The bispecific antigen-binding molecule of claim 29, wherein the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 24.

31. The bispecific antigen-binding molecule of any one of claims 12-30, wherein 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, or
- (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26.

32. The bispecific antigen-binding molecule of any one of claims 12-31, wherein the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 27.

33. The bispecific antigen-binding molecule of claim 32, wherein the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 27.

34. The bispecific antigen-binding molecule of any one of claims 12-33, wherein 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.

35. The bispecific antigen-binding molecule of any one of claims 12-34, 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.

36. The bispecific antigen-binding molecule of claim 35, wherein 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.

37. The bispecific antigen-binding molecule of any one of claims 12-36, wherein the VL_{B1} region and/or the VL_{B2} region comprises one or more liability fixed residues.

38. The bispecific antigen-binding molecule of claim 37, wherein the one or more liability fixed residues comprises the amino acid substitution of N30S.

39. The bispecific antigen-binding molecule of any one of claims 12-38, wherein the VH_{B1} region and/or the VH_{B2} region comprises one or more liability fixed residues.

40. The bispecific antigen-binding molecule of claim 39, wherein the one or more liability fixed residues comprises one or more amino acid substitutions selected from the group consisting of N54E, D98A, and D98T.

41. The bispecific antigen-binding molecule of any one of claims 12-18, 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, or
- (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 32.

42. The bispecific antigen-binding molecule of any one of claims 12-18 or 41, wherein the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 33.

43. The bispecific antigen-binding molecule of claim 42, wherein the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 33.

44. The bispecific antigen-binding molecule of any one of claims 12-18 or 41-43, wherein 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.

45. The bispecific antigen-binding molecule of any one of claims 12-18 or 41-44, wherein the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 25.

46. The bispecific antigen-binding molecule of claim 45, wherein the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 25.

47. The bispecific antigen-binding molecule of any one of claims 12-18 or 41-46, wherein 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.

48. The bispecific antigen-binding molecule of any one of claims 12-18 or 41-47, 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.

49. The bispecific antigen-binding molecule of claim 48, wherein 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.

50. The bispecific antigen-binding molecule of any one of claims 12-18 or 41-49, wherein 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: 32.

51. The bispecific antigen-binding molecule of any one of claims 12-18 or 41-50, wherein the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 33.

52. The bispecific antigen-binding molecule of claim 51, wherein the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 33.

53. The bispecific antigen-binding molecule of any one of claims 12-18 or 41-52, wherein 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, or
- (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 23.

54. The bispecific antigen-binding molecule of any one of claims 12-18 or 41-53, wherein the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 25.

55. The bispecific antigen-binding molecule of claim 54, wherein the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 25.

56. The bispecific antigen-binding molecule of any one of claims 12-18 or 41-55, wherein 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.

57. The bispecific antigen-binding molecule of any one of claims 12-18 or 41-56, 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.

58. The bispecific antigen-binding molecule of claim 57, wherein 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.

59. The bispecific antigen-binding molecule of any one of claims 12-18, 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, or
- (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 37.

60. The bispecific antigen-binding molecule of any one of claims 12-18 or 59, wherein the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 41.

61. The bispecific antigen-binding molecule of claim 60, wherein the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 41.

62. The bispecific antigen-binding molecule of any one of claims 12-18 or 59-61, wherein 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, or
- (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26.

63. The bispecific antigen-binding molecule of any one of claims 12-18 or 59-62, wherein the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 48.

64. The bispecific antigen-binding molecule of claim 63, wherein the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 48.

65. The bispecific antigen-binding molecule of any one of claims 12-18 or 59-64, wherein 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: 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.

66. The bispecific antigen-binding molecule of any one of claims 12-18 or 59-65, 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: 48.

67. The bispecific antigen-binding molecule of claim 66, wherein 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: 48.

68. The bispecific antigen-binding molecule of any one of claims 12-18 or 59-67, wherein 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, or
- (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 37.

69. The bispecific antigen-binding molecule of any one of claims 12-18 or 59-68, wherein the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 41.

70. The bispecific antigen-binding molecule of claim 69, wherein the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 41.

71. The bispecific antigen-binding molecule of any one of claims 12-18 or 59-70, wherein 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, or
- (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26.

72. The bispecific antigen-binding molecule of any one of claims 12-18 or 59-71, wherein the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 48.

73. The bispecific antigen-binding molecule of claim 72, wherein the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 48.

74. The bispecific antigen-binding molecule of any one of claims 12-17 or 59-73, wherein 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: 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.

75. The bispecific antigen-binding molecule of any one of claims 12-18 or 59-74, 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: 48.

76. The bispecific antigen-binding molecule of claim 75, wherein 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: 48.

77. The bispecific antigen-binding molecule of any one of claims 12-18, 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, or
- (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 43.

78. The bispecific antigen-binding molecule of any one of claims 12-18 or 77, wherein the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 44.

79. The bispecific antigen-binding molecule of claim 78, wherein the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 44.

80. The bispecific antigen-binding molecule of any one of claims 12-18 or 77-79, wherein 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, or
- (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26.

81. The bispecific antigen-binding molecule of any one of claims 12-18 or 77-80, wherein 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.

82. The bispecific antigen-binding molecule of claim 81, wherein the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 48.

83. The bispecific antigen-binding molecule of any one of claims 12-18 or 77-82, wherein 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.

84. The bispecific antigen-binding molecule of any one of claims 12-18 or 77-83, 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.

85. The bispecific antigen-binding molecule of claim 84, wherein 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.

86. The bispecific antigen-binding molecule of any one of claims 12-18 or 77-85, wherein 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, or
- (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 43.

87. The bispecific antigen-binding molecule of any one of claims 12-18 or 77-86, wherein the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 44.

88. The bispecific antigen-binding molecule of claim 87, wherein the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 44.

89. The bispecific antigen-binding molecule of any one of claims 12-18 or 77-88, wherein 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, or
- (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26.

90. The bispecific antigen-binding molecule of any one of claims 12-18 or 77-89, wherein the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 48.

91. The bispecific antigen-binding molecule of claim 90, wherein the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 48.

92. The bispecific antigen-binding molecule of any one of claims 12-18 or 77-91, wherein 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.

93. The bispecific antigen-binding molecule of any one of claims 12-18 or 77-92, 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.

94. The bispecific antigen-binding molecule of claim 93, wherein 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.

95. The bispecific antigen-binding molecule of any one of claims 12-18, 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, or
- (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 37.

96. The bispecific antigen-binding molecule of any one of claims 12-18 or 95, wherein the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 41.

97. The bispecific antigen-binding molecule of claim 96, wherein the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 41.

98. The bispecific antigen-binding molecule of any one of claims 12-18 or 95-97, wherein 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, or
- (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26.

99. The bispecific antigen-binding molecule of any one of claims 12-18 or 95-98, wherein the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 49.

100. The bispecific antigen-binding molecule of claim 99, wherein the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 49.

101. The bispecific antigen-binding molecule of any one of claims 12-18 or 95-100, wherein 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.

102. The bispecific antigen-binding molecule of any one of claims 12-18 or 95-101, 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.

103. The bispecific antigen-binding molecule of claim 102, wherein 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.

104. The bispecific antigen-binding molecule of any one of claims 12-18 or 95-103, wherein 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, or
- (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 37.

105. The bispecific antigen-binding molecule of any one of claims 12-18 or 95-104, wherein the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 41.

106. The bispecific antigen-binding molecule of claim 105, wherein the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 41.

107. The bispecific antigen-binding molecule of any one of claims 12-18 or 95-106, wherein 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, or
- (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26.

108. The bispecific antigen-binding molecule of any one of claims 12-18 or 95-107, wherein the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 49.

109. The bispecific antigen-binding molecule of claim 108, wherein the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 49.

110. The bispecific antigen-binding molecule of any one of claims 12-18 or 95-109, wherein 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.

111. The bispecific antigen-binding molecule of any one of claims 12-18 or 95-110, 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.

112. The bispecific antigen-binding molecule of claim 111, wherein 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.

113. The bispecific antigen-binding molecule of any one of claims 12-18, 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, or
- (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 43.

114. The bispecific antigen-binding molecule of any one of claims 12-18 or 113, wherein the VH_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 44.

115. The bispecific antigen-binding molecule of claim 114, wherein the VH_{B1} region comprises the amino acid sequence of SEQ ID NO: 44.

116. The bispecific antigen-binding molecule of any one of claims 12-18 or 113-115, wherein 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, or
- (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26.

117. The bispecific antigen-binding molecule of any one of claims 12-18 or 113-116, wherein the VL_{B1} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 49.

118. The bispecific antigen-binding molecule of claim 117, wherein the VL_{B1} region comprises the amino acid sequence of SEQ ID NO: 49.

119. The bispecific antigen-binding molecule of any one of claims 12-18 or 113-118, wherein 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: 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.

120. The bispecific antigen-binding molecule of any one of claims 12-18 or 113-119, 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: 49.

121. The bispecific antigen-binding molecule of claim 120, wherein 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: 49.

122. The bispecific antigen-binding molecule of any one of claims 12-18 or 113-121, wherein 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, or
- (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 43.

123. The bispecific antigen-binding molecule of any one of claims 12-18 or 113-122, wherein the VH_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 44.

124. The bispecific antigen-binding molecule of claim 123, wherein the VH_{B2} region comprises the amino acid sequence of SEQ ID NO: 44.

125. The bispecific antigen-binding molecule of any one of claims 12-18 or 113-124, wherein 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, or
- (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 26.

126. The bispecific antigen-binding molecule of any one of claims 12-18 or 113-125, wherein the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 49.

127. The bispecific antigen-binding molecule of claim 126, wherein the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 49.

128. The bispecific antigen-binding molecule of any one of claims 12-18 or 113-127, wherein 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: 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.

129. The bispecific antigen-binding molecule of any one of claims 12-18 or 113-128, 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: 49.

130. The bispecific antigen-binding molecule of claim 129, wherein 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.

131. The bispecific antigen-binding molecule of any one of claims 11-130, 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, or
- (c) an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 3.

132. The bispecific antigen-binding molecule of any one of claims 11-131, wherein the VH_A region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 7.

133. The bispecific antigen-binding molecule of claim 132, wherein the VH_A region comprises the amino acid sequence of SEQ ID NO: 7.

134. The bispecific antigen-binding molecule of any one of claims 11-133, wherein 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, or
- (c) an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 6.

135. The bispecific antigen-binding molecule of any one of claims 11-134, wherein the VL_A region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 8.

136. The bispecific antigen-binding molecule of claim 135, wherein the VL_A region comprises the amino acid sequence of SEQ ID NO: 8.

137. The bispecific antigen-binding molecule of any one of claims 11-136, wherein the VHA 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 VLA 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.

138. The bispecific antigen-binding molecule of any one of claims 11-137, wherein the VHA region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 7, and the VLA region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 8.

139. The bispecific antigen-binding molecule of claim 138, wherein the VHA region comprises the amino acid of SEQ ID NO: 7, and the VLA region comprises the amino acid sequence of SEQ ID NO: 8.

140. 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: 22,
- (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.

141. The bispecific antigen-binding molecule of claim 140, 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.

142. The bispecific antigen-binding molecule of claim 141, 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.

143. 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.

144. The bispecific antigen-binding molecule of claim 143, 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.

145. The bispecific antigen-binding molecule of claim 144, 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: 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.

146. 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: 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.

147. The bispecific antigen-binding molecule of claim 146, 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: 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: 41, and the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 48.

148. The bispecific antigen-binding molecule of claim 147, 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: 48; 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: 48.

149. 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.

150. The bispecific antigen-binding molecule of claim 149, 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.

151. The bispecific antigen-binding molecule of claim 150, 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: 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.

152. 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.

153. The bispecific antigen-binding molecule of claim 152, 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.

154. The bispecific antigen-binding molecule of claim 153, 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.

155. 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: 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.

156. The bispecific antigen-binding molecule of claim 155, 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: 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: 44, and the VL_{B2} region comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 49.

157. The bispecific antigen-binding molecule of claim 156, 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: 44, 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: 44, and the VL_{B2} region comprises the amino acid sequence of SEQ ID NO: 49.

158. The bispecific antigen-binding molecule of any one of claims 1-157, wherein the Fc domain is an IgG Fc domain.

159. The bispecific antigen-binding molecule of claim 158, wherein the IgG Fc domain is an IgG₁ or IgG₄ Fc domain.

160. The bispecific antigen-binding molecule of any one of claims 1-159, wherein the Fc domain is a human Fc domain.

161. The bispecific antigen-binding molecule of any one of claims 1-160, wherein the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor and/or effector function.

162. The bispecific antigen-binding molecule of claim 161, wherein the one or more amino acid substitutions that reduces binding to an Fc receptor and/or effector function is at N297.

163. The bispecific antigen-binding molecule of claim 162, wherein the first Fc subunit and the second Fc subunit each comprise the amino acid substitution of N297G.

164. The bispecific antigen-binding molecule of any one of claims 161-163, wherein the Fc receptor is an Fcγ receptor.

165. The bispecific antigen-binding molecule of any one of claims 161-164, wherein the effector function is antibody-dependent cell-mediated cytotoxicity (ADCC).

166. The bispecific antigen-binding molecule of any one of claims 1-165, wherein the Fc domain comprises a modification configured to promote the association of the first Fc subunit with the second Fc subunit.

167. The bispecific antigen-binding molecule of claim 166, wherein 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.

168. The bispecific antigen-binding molecule of claim 167, wherein 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.

169. The bispecific antigen-binding molecule of claim 168, wherein 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.

170. The bispecific antigen-binding molecule of any one of claims 1-169, 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.

171. The bispecific antigen-binding molecule of claim 170, wherein the peptide linker is from 5 to 20 amino acids in length.

172. The bispecific antigen-binding molecule of claim 171, wherein the peptide linker comprises the amino acid sequence of SEQ ID NO: 50.

173. The bispecific antigen-binding molecule of claim 172, wherein the antigen-binding molecule comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 53.

174. The bispecific antigen-binding molecule of claim 173, wherein the antigen-binding molecule comprises an amino acid sequence having at least 95% sequence identity to any one of SEQ ID NOs: 57, 61, 81, 83, 85, and 87.

175. The bispecific antigen-binding molecule of claim 174, wherein the antigen-binding molecule comprises the amino acid sequence of any one of SEQ ID NOs: 57, 61, 81, 83, 85, and 87.

176. The bispecific antigen-binding molecule of claim 175, wherein the peptide linker comprises the amino acid sequence of SEQ ID NO: 51.

177. The bispecific antigen-binding molecule of claim 176, wherein the antigen-binding molecule comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 56.

178. The bispecific antigen-binding molecule of claim 177, wherein the antigen-binding molecule comprises an amino acid sequence having at least 95% sequence identity to any one of SEQ ID NOs: 58, 62, 82, 84, 86, and 88.

179. The bispecific antigen-binding molecule of claim 178, wherein the antigen-binding molecule comprises the amino acid sequence of any one of SEQ ID NOs: 58, 62, 82, 84, 86, and 88.

180. An isolated nucleic acid encoding the bispecific antigen-binding molecule of any one of claims 1-179.

181. A vector comprising the isolated nucleic acid of claim 180.

182. A host cell comprising the isolated nucleic acid of claim 180 or the vector of claim 181.

183. The host cell of claim 182, wherein the host cell is a mammalian cell.

184. The host cell of claim 183, wherein the mammalian cell is a Chinese hamster ovary (CHO) cell.

185. The host cell of claim 184, wherein the host cell is a prokaryotic cell.

186. The host cell of claim 185, wherein the prokaryotic cell is an *E. coli* cell.

187. A method of producing the bispecific antigen-binding molecule of any one of claims 1-179, the method comprising culturing the host cell of any one of claims 182-186 in a culture medium.

188. The method of claim 187, wherein the method further comprises recovering the bispecific antigen-binding molecule from the host cell or the culture medium.

189. A set of isolated nucleic acids encoding the bispecific antigen-binding molecule of any one of claims 1-179.

190. A set of vectors, wherein each vector of the set comprises an isolated nucleic acid of the set of isolated nucleic acids of claim 189.

191. 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 189 or a vector of the set of vectors of claim 190.

192. The set of host cells of claim 191, wherein the host cells comprise mammalian cells.

193. The set of host cells of claim 192, wherein the mammalian cells are CHO cells.

194. The set of host cells of claim 191, wherein the host cells comprise prokaryotic cells.

195. The set of host cells of claim 194, wherein the prokaryotic cells are *E. coli* cells.

196. A method of producing the bispecific antigen-binding molecule of any one of claims 1-179, the method comprising culturing the set of host cells of any one of claims 191-195 in culture medium.

197. The method of claim 196, wherein the method further comprises recovering the bispecific antigen-binding molecule from the set of host cells or the culture medium.

198. An immunoconjugate comprising the bispecific antigen-binding molecule of any one of claims 1-179 and a cytotoxic agent.

199. A composition comprising the bispecific antigen-binding molecule of any one of claims 1-179.

200. The composition of claim 199, further comprising a pharmaceutically acceptable carrier, excipient, or diluent.

201. The composition of claim 199 or 200, wherein the composition is a pharmaceutical composition.

202. The composition of any one of claims 199-201, wherein the composition further comprises a PD-1 axis binding antagonist or an additional therapeutic agent.

203. The bispecific antigen-binding molecule of any one of claims 1-179 for use as a medicament.

204. The bispecific antigen-binding molecule of any one of claims 1-179 for use in treating or delaying progression of a HER2-positive cancer in a subject in need thereof.

205. The bispecific antigen-binding molecule of any one of claims 1-179 for use in enhancing immune function in a subject having a HER2-positive cancer.

206. The bispecific antigen-binding molecule of claim 205, 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.

207. The bispecific antigen-binding molecule of any one of claims 204-206, 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.

208. Use of the bispecific antigen-binding molecule of any one of claims 1-179 in the manufacture of a medicament for treating or delaying progression of a HER2-positive cancer.

209. Use of the bispecific antigen-binding molecule of any one of claims 1-179 in the manufacture of a medicament for enhancing immune function in a subject having a HER2-positive cancer.

210. The use of claim 208 or 209, 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.

211. The use of any one of claims 208-210, 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.

212. A method of treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, the method comprising administering to the subject the bispecific antigen-binding molecule of any one of claims 1-179.

213. A method of enhancing immune function in a subject having a HER2-positive cancer, the method comprising administering to the subject the bispecific antigen-binding molecule of any one of claims 1-179.

214. The method of claim 212 or 213, 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.

215. The method of any one of claims 212-214, 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.

216. A method of treating or delaying the progression of a HER2-positive cancer in a subject in need thereof, the method comprising:

- (a) determining an expression of HER2 on a tumor cell, wherein the tumor cell expresses HER2 at an average copy number of 200,000 or more copies per cell; and
- (b) administering to the subject the bispecific antigen-binding molecule of any one of claims 1-179.

217. A method of enhancing immune function in a subject having a HER2-positive cancer, the method comprising:

- (a) determining an expression of HER2 on a tumor cell, wherein the tumor cell expresses HER2 at an average copy number of 200,000 or more copies per cell; and
- (b) administering to the subject the bispecific antigen-binding molecule of any one of claims 1-179.

218. The method of claim 216 or 217, 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.

219. The method of any one of claims 212-218, wherein the bispecific antigen-binding molecule is administered to the subject in a dosage of about 0.01 mg/kg to about 10 mg/kg.

220. The method of claim 219, wherein the bispecific antigen-binding molecule is administered to the subject in a dosage of about 0.1 mg/kg to about 10 mg/kg.

221. The method of claim 220, wherein the bispecific antigen-binding molecule is administered to the subject in a dosage of about 1 mg/kg.

222. The method of any one of claims 212-221, further comprising administering to the subject a PD-1 axis binding antagonist and/or an additional therapeutic agent.

223. The method of claim 222, wherein the PD-1 axis binding antagonist or additional therapeutic agent is administered prior to or subsequent to the administration of the bispecific antigen-binding molecule.

224. The method of claim 222, wherein the PD-1 axis binding antagonist additional therapeutic agent is administered concurrently with the bispecific antigen-binding molecule.

225. The method of any one of claims 212-224, 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.

226. The method of claim 225, wherein the PD-1 axis binding antagonist is a PD-L1 binding antagonist.

227. The method of claim 226, wherein the PD-L1 binding antagonist is selected from the group consisting of MPDL3280A (atezolizumab), YW243.55.S70, MDX-1105, MEDI4736 (durvalumab), and MSB0010718C (avelumab).

228. The method of claim 225, wherein the PD-1 axis binding antagonist is a PD-1 binding antagonist.

229. The method of claim 228, wherein 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.

230. The method of claim 225, wherein the PD-1 axis binding antagonist is a PD-L2 binding antagonist.

231. The method of claim 230, wherein the PD-L2 binding antagonist is an antibody or an immunoadhesin.

232. The method of any one of claims 212-231, wherein the bispecific antigen-binding molecule is administered subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

233. The method of claim 232, wherein the bispecific antigen-binding molecule is administered subcutaneously.

234. The method of claim 232, wherein the bispecific antigen-binding molecule is administered intravenously.

235. The method of any one of claims 212-234, wherein the subject is a human.

236. A kit comprising:

- (a) the composition of any one of claims 199-202; and
- (b) a package insert comprising instructions for administering the composition to a subject to treat or delay progression of a HER2-positive cancer.

237. The kit of claim 236, 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.