

WHAT IS CLAIMED IS:

1. A protein comprising:
 - (a) a first Fc polypeptide that is fused at the N-terminus to an Fd portion of a Fab;
 - (b) a second Fc polypeptide that is fused at the N-terminus to a single-chain variable fragment (scFv), wherein the first and second Fc polypeptides form an Fc dimer; and
 - (c) a light chain polypeptide that pairs with the Fd portion recited in (a) to form a Fab,wherein the Fab binds to subdomain II of human HER2 and the scFv binds to subdomain IV of human HER2, or wherein the Fab binds to subdomain IV of human HER2 and the scFv binds to subdomain II of human HER2.
2. The protein of claim 1, wherein the Fab binds to subdomain II of human HER2 and the scFv binds to subdomain IV of human HER2.
3. The protein of claim 1, wherein the Fab binds to subdomain IV of human HER2 and the scFv binds to subdomain II of human HER2.
4. The protein of any one of claims 1 to 3, wherein the second Fc polypeptide is fused to the scFv via a first linker.
5. The protein of claim 4, wherein the first linker has a length from 1 to 20 amino acids.
6. The protein of claim 4 or 5, wherein the first linker comprises the sequence GGGGSGGGGS (SEQ ID NO:118).
7. The protein of any one of claims 1 to 6, wherein the scFv comprises a V_L region and a V_H region that are connected via a second linker.
8. The protein of claim 7, wherein the second linker has a length from 1 to 20 amino acids.
9. The protein of claim 7 or 8, wherein the second linker comprises a sequence of any one of GGSGGGSGGGSGGGSGGGSG (SEQ ID NO:116; (GGSG)₅),

GGGGS (SEQ ID NO:117; G₄S), GGGGSGGGGS (SEQ ID NO:118; (G₄S)₂), GGGGSGGGSGGGGS (SEQ ID NO:119; (G₄S)₃), GGGGSGGGSGGGG (SEQ ID NO:120; (G₄S)₂-G₄), GGGGSGGGSGG (SEQ ID NO:121), GGGGSGGGGS (SEQ ID NO:122), and GGGGSGGGGSGGGGS (SEQ ID NO:123).

10. The protein of any one of claims 1 to 9, wherein the first Fc polypeptide and/or the second Fc polypeptide specifically binds to a transferrin receptor.

11. The protein of any one of claims 1 to 10, wherein the first Fc polypeptide and the second Fc polypeptide each comprises modifications that promote heterodimerization.

12. The protein of claim 11, wherein the first Fc polypeptide comprises a T366W substitution and the second Fc polypeptide comprises T366S, L368A, and Y407V substitutions, according to EU numbering.

13. The protein of claim 11, wherein the first Fc polypeptide comprises T366S, L368A, and Y407V substitutions and the second Fc polypeptide comprises a T366W substitution, according to EU numbering.

14. The protein of any one of claims 1 to 13, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises modifications that reduce effector function.

15. The protein of claim 14, wherein the modifications that reduce effector function are L234A and L235A substitutions, according to EU numbering.

16. The protein of any one of claims 1 to 15, wherein a hinge region or a portion thereof is linked to the N-terminus of the first Fc polypeptide and/or the second Fc polypeptide.

17. The protein of any one of claims 1 to 16, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises a sequence having at least 90% identity to a sequence selected from the group consisting of SEQ ID NOS:131-149.

18. The protein of any one of claims 1 to 17, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises a sequence having at least 90% identity to a sequence selected from SEQ ID NOS:135-139.

19. The protein of any one of claims 1 to 18, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises Tyr at position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to EU numbering, and a sequence having at least 90% identity to a sequence selected from SEQ ID NOS:135-139.

20. The protein of any one of claims 1 to 19, wherein the first Fc polypeptide comprises Ala at position 234, Ala at position 235, Trp at position 366, Tyr at position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:137, and

the second Fc polypeptide comprises Ser at position 366, Ala at position 368, and Val at position 407, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:133.

21. The protein of any one of claims 1 to 19, wherein the first Fc polypeptide comprises Ser at position 366, Ala at position 368, and Val at position 407, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:133, and

the second Fc polypeptide comprises Ala at position 234, Ala at position 235, Trp at position 366, Tyr at position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:137.

22. The protein of any one of claims 1 to 21, wherein:

(i) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:1, (b) comprises a sequence having at least 90% identity to the sequence of SEQ

ID NO:21, and (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(ii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:2, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:20, and (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(iii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:3, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:19, and (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(iv) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:4, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:18, and (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(v) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:6, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:15 or 17, and (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(vi) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:7, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:14, and (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(vii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:8, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:13, and (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(viii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:9, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:11 or 12, and (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(ix) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:1, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:22, and (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(x) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:5, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:18, and (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25.

23. The protein of claim 22, wherein the first Fc polypeptide comprises Leu at positions 234 and 235, according to EU numbering.

24. The protein of claim 22 or 23, wherein the second Fc polypeptide comprises Leu at positions 234 and 235, according to EU numbering.

25. A protein comprising:

(a) a first Fc polypeptide that is fused at the N-terminus to an Fd portion of a Fab;

(b) a second Fc polypeptide that is fused at the N-terminus to an Fd portion of a Fab, wherein the first and second Fc polypeptides form an Fc dimer; and

(c) two light chain polypeptides that each pairs with each Fd portion recited in (a) and (b) to form a Fab;

wherein the first Fc polypeptide and/or the second Fc polypeptide is fused at the C-terminus to an scFv, or

wherein the Fd portion in (a) and/or (b) is fused at the N-terminus to an scFv, or

wherein the first Fc polypeptide or the second Fc polypeptide is fused at the C-terminus to an scFv and the Fd portion in (a) or (b) is fused at the N-terminus to an scFv, and

wherein the Fab binds to subdomain II of human HER2 and the scFv binds to subdomain IV of human HER2, or wherein the Fab binds to subdomain IV of human HER2 and the scFv binds to subdomain II of human HER2.

26. The protein of claim 25, wherein the first Fc polypeptide and/or the second Fc polypeptide is fused at the C-terminus to the scFv.

27. The protein of claim 25, wherein the Fd portion in (a) and/or (b) is fused at the N-terminus to the scFv.

28. The protein of claim 25, wherein the first Fc polypeptide or the second Fc polypeptide is fused at the C-terminus to the scFv and the Fd portion in (a) or (b) is fused at the N-terminus to the scFv.

29. The protein of any one of claims 25 to 28, wherein the Fab binds to subdomain II of human HER2 and the scFv binds to subdomain IV of human HER2.

30. The protein of any one of claims 25 to 28, wherein the Fab binds to subdomain IV of human HER2 and the scFv binds to subdomain II of human HER2.

31. The protein of any one of claims 25 to 30, wherein the scFv that is fused to the first Fc polypeptide and/or the second Fc polypeptide comprises identical sequences.

32. The protein of any one of claims 25 to 30, wherein the scFv that is fused to the Fd portion in (a) and/or (b) comprises identical sequences.

33. The protein of any one of claims 25 to 32, wherein the first Fc polypeptide and/or the second Fc polypeptide is fused to the scFv via a first linker.

34. The protein of any one of claims 25 to 33, wherein the Fd portion in (a) and/or (b) is fused to the scFv via a first linker.

35. The protein of claim 33 or 34, wherein the first linker has a length from 1 to 20 amino acids.

36. The protein of any one of claims 33 to 35, wherein the first linker comprises a sequence of any one of GSGSGSGSGSGSGSGSGSG (SEQ ID NO:116; (GSG)₅), GGGGS (SEQ ID NO:117; G₄S), GGGSGGGGS (SEQ ID NO:118; (G₄S)₂), GGGSGGGSGGGGS (SEQ ID NO:119; (G₄S)₃), GGGSGGGSGGGG (SEQ ID NO:120; (G₄S)₂-G₄), GGGSGGGSGG (SEQ ID NO:121), GGGSGGGGS (SEQ ID NO:122), and GGGSGGGSGGGGS (SEQ ID NO:123).

37. The protein of any one of claims 25 to 36, wherein the scFv comprises a V_L region and a V_H region that are connected via a second linker.

38. The protein of claim 37, wherein the second linker has a length from 1 to 20 amino acids.

39. The protein of claim 37 or 38, wherein the second linker comprises a sequence of any one of GGS₃GGGSGGGSGGGSG (SEQ ID NO:116; (GSG)₃), GGGGS (SEQ ID NO:117; G₄S), GGGSGGGGS (SEQ ID NO:118; (G₄S)₂), GGGSGGGSGGGGS (SEQ ID NO:119; (G₄S)₃), GGGSGGGSGGGG (SEQ ID NO:120; (G₄S)₂-G₄), GGGSGGGSGG (SEQ ID NO:121), GGGSGGGGS (SEQ ID NO:122), and GGGSGGGGGSGGGGS (SEQ ID NO:123).

40. The protein of any one of claims 25 to 39, wherein the first Fc polypeptide and/or the second Fc polypeptide specifically binds to a transferrin receptor.

41. The protein of any one of claims 25 to 40, wherein the first Fc polypeptide and the second Fc polypeptide each comprises modifications that promote heterodimerization.

42. The protein of claim 41, wherein the first Fc polypeptide comprises a T366W substitution and the second Fc polypeptide comprises T366S, L368A, and Y407V substitutions, according to EU numbering.

43. The protein of claim 41, wherein the first Fc polypeptide comprises T366S, L368A, and Y407V substitutions and the second Fc polypeptide comprises a T366W substitution, according to EU numbering.

44. The protein of any one of claims 25 to 43, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises modifications that reduce effector function.

45. The protein of claim 44, wherein the modifications that reduce effector function are L234A and L235A substitutions, according to EU numbering.

46. The protein of any one of claims 25 to 45, wherein a hinge region or a portion thereof is linked to the N-terminus of the first Fc polypeptide and/or the second Fc polypeptide.

47. The protein of any one of claims 25 to 46, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises a sequence having at least 90% identity to a sequence selected from the group consisting of SEQ ID NOS:131-149.

48. The protein of any one of claims 25 to 47, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises a sequence having at least 90% identity to a sequence selected from SEQ ID NOS:135-139.

49. The protein of any one of claims 25 to 48, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises Tyr at position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to EU numbering, and a sequence having at least 90% identity to a sequence selected from SEQ ID NOS:135-139.

50. The protein of any one of claims 25 to 49, wherein the first Fc polypeptide comprises Ala at position 234, Ala at position 235, Trp at position 366, Tyr at position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:137, and

the second Fc polypeptide comprises Ser at position 366, Ala at position 368, and Val at position 407, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:133.

51. The protein of any one of claims 25 to 49, wherein the first Fc polypeptide comprises Ser at position 366, Ala at position 368, and Val at position 407, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:133, and

the second Fc polypeptide comprises Ala at position 234, Ala at position 235, Trp at position 366, Tyr at position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:137.

52. The protein of any one of claims 25 to 51, wherein:

(i) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:27 or 28, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:4, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(ii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:29, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:3, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(iii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:30, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:2, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(iv) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:31, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:1, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(v) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:33 or 34, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:9, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(vi) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:35, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:8, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(vii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:36, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:7, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(viii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:37 or 39, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:6, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(ix) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:37, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:6, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(x) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:157, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:6, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26.

53. The protein of any one of claims 25 to 51, wherein:

(i) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:27 or 28, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:31, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(ii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:29, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:30, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(iii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:33 or 34, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:37 or 39, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(iv) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:35, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:36, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(v) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:33, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:38, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26.

54. The protein of any one of claims 25 to 51, wherein:

(i) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:40, (b) comprises a sequence having at least 90% identity to the sequence of

SEQ ID NO:4, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(ii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:41, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:3, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(iii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:42, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:2, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(iv) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:43, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:1, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(v) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:45 or 46, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:9, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(vi) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:47, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:8, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(vii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:48, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:7, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(viii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:49, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:6, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(ix) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:44, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:1, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(x) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:50, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:6, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(xi) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:156, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:6, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26.

55. The protein of any one of claims 25 to 51, wherein:

(i) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:40, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:43, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(ii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:41, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:42, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(iii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:45, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:49, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(iv) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:47, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:48, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(v) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:45, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:50, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(vi) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:46, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:156, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26.

56. The protein of any one of claims 25 to 51, wherein the first Fc polypeptide or the second Fc polypeptide is fused at the C-terminus to the scFv and the Fd portion in (a) or (b) is fused at the N-terminus to the scFv, and wherein:

(i) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:40, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:31, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(ii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:41, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:30, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(iii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:42, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:29, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(iv) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:43, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:27 or 28, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(v) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:45, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:37 or 39, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(vi) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:47, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:36, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(vii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:48, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:35, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(viii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:49, (b) comprises a sequence having at least 90% identity to the sequence of

SEQ ID NO:33 or 34, and each of the two light chain polypeptides in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26.

57. The protein of any one of claims 52 to 56, wherein the first Fc polypeptide comprises Leu at positions 234 and 235, according to EU numbering.

58. The protein of any one of claims 52 to 57, wherein the second Fc polypeptide comprises Leu at positions 234 and 235, according to EU numbering.

59. A protein comprising:

(a) a first Fc polypeptide that is fused at the N-terminus to an Fd portion of a Fab;

(b) a second Fc polypeptide that is fused at the N-terminus to an Fd portion of a Fab, wherein the first and second Fc polypeptides form an Fc dimer; and

(c) two light chain polypeptides that each pairs with each Fd portion recited in (a) and (b) to form a Fab;

wherein one or both of the light chain polypeptides are fused at the N-terminus to an scFv, or

wherein one or both of the light chain polypeptides are fused at the C-terminus to an scFv, or

wherein a first light chain polypeptide is fused at the N-terminus to an scFv and the second light chain polypeptide is fused at the C-terminus to an scFv, and

wherein the Fab binds to subdomain II of human HER2 and the scFv binds to subdomain IV of human HER2, or wherein Fab binds to subdomain IV of human HER2 and the scFv binds to subdomain II of human HER2.

60. The protein of claim 59, wherein one or both of the light chain polypeptides are fused at the N-terminus to the scFv.

61. The protein of claim 59, wherein one or both of the light chain polypeptides are fused at the C-terminus to the scFv.

62. The protein of claim 59, wherein a first light chain polypeptide is fused at the N-terminus to the scFv and a second light chain polypeptide is fused at the C-terminus to the scFv.

63. The protein of any one of claims 59 to 62, wherein the Fab binds to subdomain II of human HER2 and the scFv binds to subdomain IV of human HER2.

64. The protein of any one of claims 59 to 62, wherein the Fab binds to subdomain IV of human HER2 and the scFv binds to subdomain II of human HER2.

65. The protein of any one of claims 59 to 64, wherein the scFv that is fused to one or both of the light chain polypeptides comprises identical sequences.

66. The protein of any one of claims 59 to 65, wherein the one or both of the light chain polypeptides are fused to the scFv via a first linker.

67. The protein of claim 66, wherein the first linker has a length from 1 to 20 amino acids.

68. The protein of claim 66 or 67, wherein the first linker comprises a sequence of any one of GGSGGGSGGGSGGGSGGGSG (SEQ ID NO:116; (GGSG)₅), GGGGS (SEQ ID NO:117; G₄S), GGGSGGGGS (SEQ ID NO:118; (G₄S)₂), GGGSGGGSGGGGS (SEQ ID NO:119; (G₄S)₃), GGGSGGGSGGGG (SEQ ID NO:120; (G₄S)₂-G₄), GGGSGGGSGG (SEQ ID NO:121), GGGSGGGGS (SEQ ID NO:122), and GGGSGGGGGSGGGGS (SEQ ID NO:123).

69. The protein of any one of claims 59 to 68, wherein the scFv comprises a V_L region and a V_H region that are connected via a second linker.

70. The protein of claim 69, wherein the second linker has a length from 1 to 20 amino acids.

71. The protein of claim 69 or 70, wherein the second linker comprises a sequence of any one of GGSGGGSGGGSGGGSGGGSG (SEQ ID NO:116; (GGSG)₅), GGGGS (SEQ ID NO:117; G₄S), GGGSGGGGS (SEQ ID NO:118; (G₄S)₂), GGGSGGGSGGGGS (SEQ ID NO:119; (G₄S)₃), GGGSGGGSGGGG (SEQ ID NO:120; (G₄S)₂-G₄), GGGSGGGSGG (SEQ ID NO:121), GGGSGGGGS (SEQ ID NO:122), and GGGSGGGGGSGGGGS (SEQ ID NO:123).

72. The protein of any one of claims 59 to 71, wherein the first Fc polypeptide and/or the second Fc polypeptide specifically binds to a transferrin receptor.

73. The protein of any one of claims 59 to 72, wherein the first Fc polypeptide and the second Fc polypeptide each comprises modifications that promote heterodimerization.

74. The protein of claim 73, wherein the first Fc polypeptide comprises a T366W substitution and the second Fc polypeptide comprises T366S, L368A, and Y407V substitutions, according to EU numbering.

75. The protein of claim 73, wherein the first Fc polypeptide comprises T366S, L368A, and Y407V substitutions and the second Fc polypeptide comprises a T366W substitution, according to EU numbering.

76. The protein of any one of claims 59 to 75, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises modifications that reduce effector function.

77. The protein of claim 76, wherein the modifications that reduce effector function are L234A and L235A substitutions, according to EU numbering.

78. The protein of any one of claims 59 to 77, wherein a hinge region or a portion thereof is linked to the N-terminus of the first Fc polypeptide and/or the second Fc polypeptide.

79. The protein of any one of claims 59 to 78, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises a sequence having at least 90% identity to a sequence selected from the group consisting of SEQ ID NOS:131-149.

80. The protein of any one of claims 59 to 79, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises a sequence having at least 90% identity to a sequence selected from SEQ ID NOS: 135-139.

81. The protein of any one of claims 59 to 80, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises Tyr at position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to

EU numbering, and a sequence having at least 90% identity to a sequence selected from SEQ ID NOS:135-139.

82. The protein of any one of claims 59 to 81, wherein the first Fc polypeptide comprises Ala at position 234, Ala at position 235, Trp at position 366, Tyr at position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:137, and

the second Fc polypeptide comprises Ser at position 366, Ala at position 368, and Val at position 407, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:133.

83. The protein of any one of claims 59 to 81, wherein the first Fc polypeptide comprises Ser at position 366, Ala at position 368, and Val at position 407, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:133, and

the second Fc polypeptide comprises Ala at position 234, Ala at position 235, Trp at position 366, Tyr at position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:137.

84. The protein of any one of claims 59 to 83, wherein:

(i) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:1, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:4, a first light chain polypeptide is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:52, and a second light chain polypeptide comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(ii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:2, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:3, a first light chain polypeptide is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:52, and a second light

chain polypeptide comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(iii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:6, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:9, a first light chain polypeptide is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:53 or 54, and a second light chain polypeptide comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(iv) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:7, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:8, a first light chain polypeptide is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:53 or 54, and a second light chain polypeptide comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26.

85. The protein of any one of claims 59 to 83, wherein:

(i) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:1, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:4, and each of the two light chain polypeptides is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:52; or

(ii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:2, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:3, and each of the two light chain polypeptides is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:52; or

(iii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:6, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:9, and each of the two light chain polypeptides is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:53 or 54; or

(iv) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:7, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:8, and each of the two light chain polypeptides is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:53 or 54.

86. The protein of any one of claims 59 to 83, wherein:

(i) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:1, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:4, a first light chain polypeptide is fused at the N-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:55, and a second light chain polypeptide comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(ii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:2, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:3, a first light chain polypeptide is fused at the N-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:55, and a second light chain polypeptide comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(iii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:6, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:9, a first light chain polypeptide is fused at the N-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:56 or 57, and a second light chain polypeptide comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(iv) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:7, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:8, a first light chain polypeptide is fused at the N-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:56 or 57, and a second light chain polypeptide comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26.

87. The protein of any one of claims 59 to 83, wherein:

(i) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:1, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:4, and each of the two light chain polypeptides is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:55; or

(ii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:2, (b) comprises a sequence having at least 90% identity to the sequence of SEQ

ID NO:3, and each of the two light chain polypeptides is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:55; or

(iii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:6, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:9, and each of the two light chain polypeptides is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:56 or 57; or

(iv) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:7, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:8, and each of the two light chain polypeptides is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:56 or 57.

88. The protein of any one of claims 59 to 83, wherein:

(i) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:1, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:4, a first light chain polypeptide is fused at the N-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:55, and a second light chain polypeptide is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:52; or

(ii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:2, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:3, a first light chain polypeptide is fused at the N-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:55, and a second light chain polypeptide is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:52; or

(iii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:6, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:9, a first light chain polypeptide is fused at the N-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:56 or 57, and a second light chain polypeptide is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:53 or 54 comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(iv) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:7, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:8, a first light chain polypeptide is fused at the N-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:56 or 57, and a second light chain polypeptide is fused at the C-terminus to the scFv and comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:53 or 54 comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26.

89. The protein of any one of claims 84 to 88, wherein the first Fc polypeptide comprises Leu at positions 234 and 235, according to EU numbering.

90. The protein of any one of claims 84 to 88, wherein the second Fc polypeptide comprises Leu at positions 234 and 235, according to EU numbering.

91. A protein comprising:

(a) a first Fc polypeptide that is fused at the N-terminus to an Fd portion of a Fab;

(b) a second Fc polypeptide that is fused at the N-terminus to an Fd portion of a Fab, wherein the first and second Fc polypeptides form an Fc dimer; and

(c) two light chain polypeptides that each pairs with each Fd portion recited in (a) and (b) to form a Fab;

wherein each of the Fd portions in (a) and (b) is fused at the N-terminus to a V_H region or a V_L region of an Fv fragment, and

wherein each of the two light chain polypeptides is fused at the N-terminus to the other of a V_H region or a V_L region of the Fv fragment, and

wherein the V_H region and the V_L region together form the Fv fragment, and

wherein the Fab binds to subdomain II of human HER2 and the Fv fragment binds to subdomain IV of human HER2, or wherein the Fab binds to subdomain IV of human HER2 and the Fv fragment binds to subdomain II of human HER2.

92. The protein of claim 91, wherein the Fab binds to subdomain II of human HER2 and the Fv fragment binds to subdomain IV of human HER2.

93. The protein of claim 91, wherein the Fab binds to subdomain IV of human HER2 and the Fv fragment binds to subdomain II of human HER2.

94. The protein of any one of claims 91 to 93, wherein each of the Fd portions in (a) and (b) is fused at the N-terminus to a V_H region or a V_L region via a first linker.

95. The protein of claim 94, wherein the first linker has a length from 1 to 20 amino acids.

96. The protein of claim 94 or 95, wherein the first linker comprises a sequence of ASTKGPSVF (SEQ ID NO:125).

97. The protein of any one of claims 91 to 96, wherein each of the two light chain polypeptides is fused at the N-terminus to a V_H region or a V_L region via a second linker.

98. The protein of claim 97, wherein the second linker has a length from 1 to 20 amino acids.

99. The protein of claim 97 or 98, wherein the second linker comprises a sequence of RTVAAPSVFI (SEQ ID NO:126).

100. The protein of any one of claims 91 to 99, wherein each of the Fd portions in (a) and (b) is fused at the N-terminus to the V_H region of an Fv fragment, and each of the two light chain polypeptides is fused at the N-terminus to the V_L region of the Fv fragment.

101. The protein of any one of claims 91 to 99, wherein the first Fc polypeptide and/or the second Fc polypeptide specifically binds to a transferrin receptor.

102. The protein of any one of claims 91 to 101, wherein the first Fc polypeptide and the second Fc polypeptide each comprises modifications that promote heterodimerization.

103. The protein of claim 102, wherein the first Fc polypeptide comprises a T366W substitution and the second Fc polypeptide comprises T366S, L368A, and Y407V substitutions, according to EU numbering.

104. The protein of claim 102, wherein the first Fc polypeptide comprises T366S, L368A, and Y407V substitutions and the second Fc polypeptide comprises a T366W substitution, according to EU numbering.

105. The protein of any one of claims 91 to 104, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises modifications that reduce effector function.

106. The protein of claim 105, wherein the modifications that reduce effector function are L234A and L235A substitutions, according to EU numbering.

107. The protein of any one of claims 91 to 106, wherein a hinge region or a portion thereof is linked to the N-terminus of the first Fc polypeptide and/or the second Fc polypeptide.

108. The protein of any one of claims 91 to 107, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises a sequence having at least 90% identity to a sequence selected from the group consisting of SEQ ID NOS:131-149.

109. The protein of any one of claims 91 to 108, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises a sequence having at least 90% identity to a sequence selected from SEQ ID NOS: 135-139.

110. The protein of any one of claims 91 to 109, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises Tyr at position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to EU numbering, and a sequence having at least 90% identity to a sequence selected from SEQ ID NOS:135-139.

111. The protein of any one of claims 91 to 110, wherein the first Fc polypeptide comprises Ala at position 234, Ala at position 235, Trp at position 366, Tyr at position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:137, and

the second Fc polypeptide comprises Ser at position 366, Ala at position 368, and Val at position 407, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:133.

112. The protein of any one of claims 91 to 110, wherein the first Fc polypeptide comprises Ser at position 366, Ala at position 368, and Val at position 407, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:133, and

the second Fc polypeptide comprises Ala at position 234, Ala at position 235, Trp at position 366, Tyr at position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:137.

113. The protein of any one of claims 91 to 112, wherein the protein comprises:

(i) a first polypeptide comprising (a) fused at the N-terminus to the V_H region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:58, a second polypeptide comprising (b) fused at the N-terminus to the V_H region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:61, and third and fourth polypeptides each comprising a light chain polypeptide fused at the N-terminus to the V_L region of the Fv fragment and each comprising a sequence having at least 90% identity to the sequence of SEQ ID NO:78; or

(ii) a first polypeptide comprising (a) fused at the N-terminus to the V_H region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:59, a second polypeptide comprising (b) fused at the N-terminus to the V_H region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:60, and third and fourth polypeptides each comprising a light chain polypeptide fused at the N-terminus to the V_L region of the Fv fragment and each comprising a sequence having at least 90% identity to the sequence of SEQ ID NO:78; or

(iii) a first polypeptide comprising (a) fused at the N-terminus to the V_H region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:63, a second polypeptide comprising (b) fused at the N-terminus to the V_H region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:66,

and third and fourth polypeptides each comprising a light chain polypeptide fused at the N-terminus to the V_L region of the Fv fragment and each comprising a sequence having at least 90% identity to the sequence of SEQ ID NO:79; or

(iv) a first polypeptide comprising (a) fused at the N-terminus to the V_H region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:64, a second polypeptide comprising (b) fused at the N-terminus to the V_H region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:65, and third and fourth polypeptides each comprising a light chain polypeptide fused at the N-terminus to the V_L region of the Fv fragment and each comprising a sequence having at least 90% identity to the sequence of SEQ ID NO:79; or

(v) a first polypeptide comprising (a) fused at the N-terminus to the V_H region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:63, a second polypeptide comprising (b) fused at the N-terminus to the V_H region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:67, and third and fourth polypeptides each comprising a light chain polypeptide fused at the N-terminus to the V_L region of the Fv fragment and each comprising a sequence having at least 90% identity to the sequence of SEQ ID NO:79.

114. The protein of any one of claims 91 to 112, wherein the protein comprises:

(i) a first polypeptide comprising (a) fused at the N-terminus to the V_L region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:68, a second polypeptide comprising (b) fused at the N-terminus to the V_L region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:71, and third and fourth polypeptides each comprising a light chain polypeptide fused at the N-terminus to the V_H region of the Fv fragment and each comprising a sequence having at least 90% identity to the sequence of SEQ ID NO:80; or

(ii) a first polypeptide comprising (a) fused at the N-terminus to the V_L region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:69, a second polypeptide comprising (b) fused at the N-terminus to the V_L region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:70, and third and fourth polypeptides each comprising a light chain polypeptide fused at the N-terminus to the V_H region of the Fv fragment and each comprising a sequence having at least 90% identity to the sequence of SEQ ID NO:80; or

(iii) a first polypeptide comprising (a) fused at the N-terminus to the V_L region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:73, a second polypeptide comprising (b) fused at the N-terminus to the V_L region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:76, and third and fourth polypeptides each comprising a light chain polypeptide fused at the N-terminus to the V_H region of the Fv fragment and each comprising a sequence having at least 90% identity to the sequence of SEQ ID NO:81; or

(iv) a first polypeptide comprising (a) fused at the N-terminus to the V_L region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:74, a second polypeptide comprising (b) fused at the N-terminus to the V_L region of the Fv fragment and a sequence having at least 90% identity to the sequence of SEQ ID NO:75, and third and fourth polypeptides each comprising a light chain polypeptide fused at the N-terminus to the V_H region of the Fv fragment and each comprising a sequence having at least 90% identity to the sequence of SEQ ID NO:81.

115. The protein of claim 113, wherein the first Fc polypeptide comprises Leu at positions 234 and 235, according to EU numbering.

116. The protein of claim 113, wherein the second Fc polypeptide comprises Leu at positions 234 and 235, according to EU numbering.

117. A protein comprising:

(a) a first Fc polypeptide that is fused at the N-terminus to an Fd portion of a Fab, and is fused at the C-terminus to a V_H region or a V_L region of an Fv fragment;

(b) a second Fc polypeptide that is fused at the N-terminus to an Fd portion of a Fab, and is fused at the C-terminus to the other of a V_H region or a V_L region recited in (a),

wherein the V_H region and the V_L region together form the Fv fragment, and wherein the first and second Fc polypeptides form an Fc dimer; and

(c) two light chain polypeptides that each pairs with each Fd portion recited in (a) and (b) to form a Fab;

wherein the Fab binds to subdomain II of human HER2 and the Fv fragment binds to subdomain IV of human HER2, or wherein the Fab binds to subdomain IV of human HER2 and the Fv fragment binds to subdomain II of human HER2.

118. The protein of claims 117, wherein the Fab binds to subdomain II of human HER2 and the Fv fragment binds to subdomain IV of human HER2.

119. The protein of claims 117, wherein the Fab binds to subdomain IV of human HER2 and the Fv fragment binds to subdomain II of human HER2.

120. The protein of any one of claims 117 to 119, wherein the first Fc polypeptide is fused to the V_H region of the Fv fragment and the second Fc polypeptide is fused to the V_L region of the Fv fragment.

121. The protein of any one of claims 117 to 119, wherein the first Fc polypeptide is fused to the V_L region of the Fv fragment and the second Fc polypeptide is fused to the V_H region of the Fv fragment.

122. The protein of any one of claims 117 to 121, wherein the first Fc polypeptide and/or the second Fc polypeptide is fused at the C-terminus to the V_H region or the V_L region via a first linker.

123. The protein of claim 122, wherein the first linker has a length from 1 to 20 amino acids.

124. The protein of claim 122 or 123, wherein the first linker comprises a sequence of any one of GGSGGGSGGGSGGGSGGGSG (SEQ ID NO:116; (GGSG)₅), GGGGS (SEQ ID NO:117; G₄S), GGGSGGGGS (SEQ ID NO:118; (G₄S)₂), GGGSGGGSGGGGS (SEQ ID NO:119; (G₄S)₃), GGGSGGGSGGGG (SEQ ID NO:120; (G₄S)₂-G₄), GGGSGGGSGG (SEQ ID NO:121), GGGSGGGGS (SEQ ID NO:122), and GGGSGGGGGSGGGGS (SEQ ID NO:123).

125. The protein of any one of claims 117 to 124, wherein the first Fc polypeptide and/or the second Fc polypeptide specifically binds to a transferrin receptor.

126. The protein of any one of claims 117 to 125, wherein the first Fc polypeptide and the second Fc polypeptide each comprises modifications that promote heterodimerization.

127. The protein of claim 126, wherein the first Fc polypeptide comprises a T366W substitution and the second Fc polypeptide comprises T366S, L368A, and Y407V substitutions, according to EU numbering.

128. The protein of claim 126, wherein the first Fc polypeptide comprises T366S, L368A, and Y407V substitutions and the second Fc polypeptide comprises a T366W substitution, according to EU numbering.

129. The protein of any one of claims 117 to 128, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises modifications that reduce effector function.

130. The protein of claim 129, wherein the modifications that reduce effector function are L234A and L235A substitutions, according to EU numbering.

131. The protein of any one of claims 117 to 130, wherein a hinge region or a portion thereof is linked to the N-terminus of the first Fc polypeptide and/or the second Fc polypeptide.

132. The protein of any one of claims 117 to 131, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises a sequence having at least 90% identity to a sequence selected from the group consisting of SEQ ID NOS:131-149.

133. The protein of any one of claims 117 to 132, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises a sequence having at least 90% identity to a sequence selected from SEQ ID NOS:135-139.

134. The protein of any one of claims 117 to 133, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises Tyr at position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to EU numbering, and a sequence having at least 90% identity to a sequence selected from SEQ ID NOS:135-139.

135. The protein of any one of claims 117 to 134, wherein the first Fc polypeptide comprises Ala at position 234, Ala at position 235, Trp at position 366, Tyr at

position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:137, and

the second Fc polypeptide comprises Ser at position 366, Ala at position 368, and Val at position 407, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:133.

136. The protein of any one of claims 117 to 134, wherein the first Fc polypeptide comprises Ser at position 366, Ala at position 368, and Val at position 407, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:133, and

the second Fc polypeptide comprises Ala at position 234, Ala at position 235, Trp at position 366, Tyr at position 384, Thr at position 386, Glu at position 387, Trp at position 388, Ser at position 389, Ser at position 413, Glu at position 415, Glu at position 416, and Phe at position 421, according to EU numbering, and a sequence having at least 90% identity to the sequence of SEQ ID NO:137.

137. The protein of any one of claims 117 to 136, wherein:

(i) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:82 or 83, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:99 or 100, and each of the two light chains in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(ii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:84, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:98, and each of the two light chains in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(iii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:85, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:97, and each of the two light chains in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(iv) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:86 or 88, (b) comprises a sequence having at least 90% identity to the sequence

of SEQ ID NO:95 or 96, and each of the two light chains in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(v) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:89 or 90, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:105 or 107, and each of the two light chains in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(vi) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:91, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:104, and each of the two light chains in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(vii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:92, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:103, and each of the two light chains in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(viii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:93, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:102, and each of the two light chains in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(ix) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:82, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:99, and each of the two light chains in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(x) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:82, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:100, and each of the two light chains in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:25; or

(xi) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:90, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:107, and each of the two light chains in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26; or

(xii) (a) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:90, (b) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:158, and each of the two light chains in (c) comprises a sequence having at least 90% identity to the sequence of SEQ ID NO:26.

138. The protein of claim 137, wherein the first Fc polypeptide comprises Leu at positions 234 and 235, according to EU numbering.

139. The protein of claim 137, wherein the second Fc polypeptide comprises Leu at positions 234 and 235, according to EU numbering.

140. A pharmaceutical composition comprising the protein of any one of claims 1 to 139 and a pharmaceutically acceptable carrier.

141. An isolated polynucleotide comprising a nucleotide sequence encoding the protein of any one of claims 1 to 139.

142. A vector comprising the polynucleotide of claim 141.

143. A host cell comprising the polynucleotide of claim 141 or the vector of claim 142.

144. A method for treating a cancer or treating brain metastasis of a cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of the protein of any one of claims 1 to 139 or the pharmaceutical composition of claim 140.

145. The method of claim 144, wherein the protein is administered in combination with a chemotherapy or radiation therapy.

146. The method of claim 144 or 145, wherein the cancer is a metastatic cancer.

147. The method of any one of claims 144 to 146, wherein the cancer is a breast cancer.

148. The method of any one of claims 144 to 147, wherein the cancer is a HER2-positive cancer.