Claims

1. A full length bispecific antibody comprising a first antigen-binding site that binds domain I of ErbB-2 and a second antigen-binding site that binds domain III of ErbB-3, wherein the antibody can reduce a ligand-induced receptor function of ErbB-3 on a ErbB-2 and ErbB-3 positive cell.

2. A bispecific antibody according to claim 1, wherein the antibody can reduce ligand-induced growth of an ErbB-2 and ErbB-3 positive cell.

3. A bispecific antibody according to claim 2, wherein the antibody can reduce ligand-induced growth of an ErbB-2 and ErbB-3 positive cell, wherein said cell has at least 100,000 ErbB-2 cell-surface receptors per cell.

4. A bispecific antibody according to any one of claims 1-3, wherein said cell is an MCF-7 cell, an SKBR-3 cell, NCI-N87 cell , an BxPC-3 cell, an BT-474 cell or a JIMT-1 cell.

5. A bispecific antibody according to any one of claims 1-4, wherein the second antigen-binding site interferes with binding of an ErbB-3 ligand to ErbB-3.

6. A full length bispecific antibody comprising a first antigen-binding site that binds ErbB-2 and a second antigen-binding site that binds ErbB-3, wherein said first antigen-binding site binds domain I of ErbB-2 and said second antigen-binding site binds domain III of ErbB-3.

7. A full length bispecific antibody comprising a first antigen-binding site that binds domain I of ErbB-2 and a second antigen-binding site that binds domain III of ErbB-3, wherein the affinity (KD) of said second antigen-binding site for an ErbB-3 positive cell is equal to, or higher than, the affinity of said first antigen-binding site for an ErbB-2 positive cell.

8. A bispecific antibody according to any one of claims 1-7, wherein the antibody can reduce a ligand-induced receptor function of ErbB-3 on a ErbB-2 and ErbB-3 positive cell.

9. A bispecific antibody according to any one of claims 1-8, wherein the antibody can reduce ligand-induced growth of an ErbB-2 and ErbB-3 positive cell.

10. A bispecific antibody according to any one of claims 1-9, wherein the affinity (KD) of said second antigen-binding site for an ErbB-3 positive cell is lower than or equal to 2.0 nM, preferably lower than or equal to 1.39 nM, more preferably lower than or equal to 0.99 nM, wherein KD is determined using steady state cell affinity measurement.

11. A bispecific antibody according to any one of claims 1-10, wherein the affinity (KD) of said first antigen-binding site for an ErbB-2 positive cell is lower than or equal to 5.0 nM, preferably lower than or equal to 4.5 nM preferably lower than or equal to 4.0 nM, wherein KD is determined using steady state cell affinity measurement.

12. A bispecific antibody according to any one of claims 1-11, wherein the affinity (KD) of said bispecific antibody for BT-474 cells is lower than or equal to 5.0 nM, preferably lower than or equal to 4.0 nM, more preferably lower than or equal to 3.2 nM, and/or wherein the affinity of said bispecific antibody for SK-BR-3 cells is lower than or equal to 5.0 nM, preferably lower than or equal to 3.0 nM, more preferably lower than or equal to 2.0 nM, wherein KD is determined using steady state cell affinity measurement.

13. An antibody according to any one of claims 1-12, wherein said ErbB-3 positive cell and/or said ErbB-2 positive cell is a BT-474 cell or a SK-BR-3 cell.

14. An antibody according to any one of claims 1-13, comprising an antigen-binding site that binds at least one amino acid of domain I of ErbB-2 selected from the group consisting of T144, T164, R166, P172, G179, S180 and R181, and surface-

exposed amino acid residues that are located within about 5 amino acid positions from T144, T164, R166, P172, G179, S180 or R181.

15. An antibody according to any one of claims 1-14, comprising an antigen-binding site that binds at least one amino acid of domain III of ErbB-3 selected from the group consisting of R426 and surface-exposed amino acid residues that are located within 11.2 Å from R426 in the native ErbB-3 protein.

16. An antibody according to any one of claims 1-15, wherein said antibody comprises at least the CDR3 sequence of an ErbB-2 specific heavy chain variable region selected from the group consisting of MF2926, MF2973, MF3004, MF3958, MF2971, MF3025, MF2916, MF3991, MF3031, and MF3003 as depicted in Figure 16A or Figure 16E.

17. An antibody according to any one of claims 1-16, wherein said antibody comprises at least the CDR3 sequence of an ErbB-3 specific heavy chain variable region selected from the group consisting of MF3178; MF3176; MF3163; MF3099; MF3307; MF6055; MF6056; MF6057; MF6058; MF6059; MF6060; MF6061; MF6062; MF6063; MF6064; MF 6065; MF6066; MF6067; MF6068; MF6069; MF6070; MF6071; MF6072; MF6073 and MF6074 as depicted in Figure 16B or Figure 16E or Figure 37.

18. An antibody according to any one of claims 1-17, wherein said antibody comprises at least the CDR1, CDR2 and CDR3 sequences of an ErbB-2 specific heavy chain variable region selected from the group consisting of MF2926,; MF2973, MF3004, MF3958, MF2971, MF3025, MF2916, MF3991, MF3031, and MF3003 as depicted in Figure 16A or Figure 16E, or wherein said antibody comprises CDR sequences that differ in at most 3 amino acids, preferably in at most 2 amino acids, preferably in at most 1 amino acid from the CDR1, CDR2 and CDR3 sequences of MF2926,; MF2973, MF3004, MF3958, MF2971, MF3025, MF2916, MF3991, MF3031, and MF3003.

19. An antibody according to any one of claims 1-18, wherein said antibody comprises at least the CDR1, CDR2 and CDR3 sequences of an ErbB-3 specific

heavy chain variable region selected from the group consisting of MF3178; MF3176; MF3163; MF3099; MF3307; MF6055; MF6056; MF6057; MF6058; MF6059; MF6060; MF6061; MF6062; MF6063; MF6064; MF 6065; MF6066; MF6067; MF6068; MF6069; MF6070; MF6071; MF6072; MF6073 and MF6074 as depicted in Figure 16B or Figure 16E or Figure 37, or wherein said antibody comprises CDR sequences that differ in at most 3 amino acids, preferably in at most 2 amino acids, preferably in at most 1 amino acid from the CDR1, CDR2 and CDR3 sequences of MF3178; MF3176; MF3163; MF3099; MF3307; MF6055; MF6056; MF6057; MF6058; MF6059; MF6060; MF6061; MF6062; MF6063; MF6064; MF 6065; MF6066; MF6067; MF6068; MF6069; MF6070; MF6071; MF6072; MF6073 or MF6074.

20. An antibody according to any one of claims 1-19, wherein said antibody comprises an ErbB-2 specific heavy chain variable region sequence selected from the group consisting of the heavy chain variable region sequences of MF2926, MF2973, MF3004, MF3958, MF2971, MF3025, MF2916, MF3991, MF3031, and MF3003 as depicted in Figure 16A or Figure 16E, or wherein said antibody comprises a heavy chain variable region sequence that differs in at most 15 amino acids from the heavy chain variable region sequences of MF2926,; MF2973, MF3004, MF3958, MF2971, MF3025, MF2916, MF3991, MF3031, and MF3003.

21. An antibody according to any one of claims 1-20, wherein said antibody comprises an ErbB-3 specific heavy chain variable region sequence selected from the group consisting of the heavy chain variable region sequences of MF3178; MF3176; MF3163; MF3099; MF3307; MF6055; MF6056; MF6057; MF6058; MF6059; MF6060; MF6061; MF6062; MF6063; MF6064; MF 6065; MF6066; MF6067; MF6068; MF6069; MF6070; MF6071; MF6072; MF6073 and MF6074 as depicted in Figure 16B or Figure 16E or Figure 37, or wherein said antibody comprises a heavy chain variable region sequence that differs in at most 15 amino acids from the heavy chain variable region sequences of MF3178; MF3176; MF3163; MF3099; MF3307; MF6055; MF6056; MF6057; MF6058; MF6059; MF6060; MF6061; MF6062; MF6063; MF6064; MF 6065; MF6066; MF6067; MF6068; MF6069; MF6070; MF6071; MF6072; MF6073 or MF6074.

22. A bispecific antibody according to claims 1-21, which exhibits antibody-dependent cell-mediated cytotoxicity (ADCC).

23. A bispecific antibody according to any one of claims 1-22, which is afucosylated in order to enhance ADCC.

24. A bispecific antibody according to any one of claims 1-23, that is a human or humanized antibody.

25. A bispecific antibody according to any one of claims 1-24, comprising two different immunoglobulin heavy chains with compatible heterodimerization domains.

26. A bispecific antibody according to claim 25, wherein said compatible heterodimerization domains are compatible immunoglobulin heavy chain CH3 heterodimerization domains.

27. A bispecific antibody according to any one of claims 1-26, wherein both arms comprise a common light chain.

28. A bispecific antibody according to claim 27, wherein said common light chain is a germline light chain, preferably a rearranged germline human kappa light chain comprising the IgVKl-39 gene segment, most preferably the rearranged germline human kappa light chain IgVKl-39*01/IGJKl*01.

29. A bispecific antibody according to any one of claims 1-28, further comprising a label, preferably a label for *in vivo* imaging.

30. A pharmaceutical composition comprising a bispecific antibody according to any one of claims 1-29.

31. Use of an antibody or pharmaceutical composition according to any one of claims 1-29 in the manufacture of a medicament for the treatment of a subject

having a ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor or at risk of having said tumor.

32. An antibody according to any one of claims 1-29, for use in the treatment of a subject having or at risk of having an ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor.

33. An antibody for use according to claim 32, wherein said bispecific antibody does not significantly affect the survival of cardiomyocytes.

34. An antibody for use according to claim 32 or 33, wherein said bispecific antibody is for use for a subject who has a cardiac function that is lower than 90% as compared to a healthy cardiac function.

35. Use of a full length bispecific antibody comprising a first antigen-binding site that binds domain I of ErbB-2 and a second antigen-binding site that binds domain III of ErbB-3, and

- one or more compounds selected from the group consisting of an inhibitor of a component of the PI3Kinase pathway, an inhibitor of a component of the MAPK pathway, a microtubuli disrupting drug and an HDAC inhibitor, preferably one or more compounds selected from the group consisting of a tyrosine kinase inhibitor, a PI3Ka inhibitor, an Akt inhibitor, an mTOR inhibitor, an Src inhibitor, vorinostat and paclitaxel in the manufacture of a medicament for the treatment of a subject having a ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor or at risk of having said tumor.

36. A full length bispecific antibody comprising a first antigen-binding site that binds domain I of ErbB-2 and a second antigen-binding site that binds domain III of ErbB-3, and at least one compound selected from the group consisting of an inhibitor of a component of the PI3Kinase pathway, an inhibitor of a component of the MAPK pathway, a microtubuli disrupting drug and an HDAC inhibitor, for use in the treatment of a ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor, preferably wherein said bispecific antibody and at least one compound selected from the group consisting of a tyrosine kinase inhibitor, a PI3Ka inhibitor, an Akt inhibitor, an

mTOR inhibitor, an Src inhibitor, vorinostat and paclitaxel, are to be administered to a subject having a ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor.

37. A use or antibody for use according to claim 35 or 36, wherein said tyrosine kinase inhibitor comprises afatinib, lapatinib and/or neratinib.

38. A use or antibody for use according to any one of claims 35 to 37, wherein said PI3K inhibitor is BYL719.

39. A use or antibody for use according to any one of claims 35 to 38, wherein said Akt inhibitor is MK-2206.

40. A use or antibody for use according to any one of claims 35 to 39, wherein said mTOR inhibitor is everolimus.

41. A use or antibody for use according to any one of claims 35 to 40, wherein said Src inhibitor is saracatinib.

42. A use or antibody for use according to any one of claims 35 to 41, wherein said microtubuli targeting drug is Paclitaxel.

43. A use or antibody for use according to any one of claims 35 to 42, wherein said HDAC inhibitor is vorinostat.

44. Use of a full length bispecific antibody comprising a first antigen-binding site that binds domain I of ErbB-2 and a second antigen-binding site that binds domain III of ErbB-3 in the manufacture of a medicament for counteracting the formation of a metastasis in a subject having a ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor, wherein said ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor cell has a heregulin expression level that is at least 60%, preferably at least 70%, more preferably at least 80%, more preferably at least 85%, more preferably at least 90% or 95% of the heregulin expression level of BXPC3 or MCF7 cells.

45. A full length bispecific antibody comprising a first antigen-binding site that binds domain I of ErbB-2 and a second antigen-binding site that binds domain III of ErbB-3 for use in the treatment or prevention of the formation of a metastasis of a ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor cell, wherein said ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor cell has a heregulin expression level that is at least 60%, preferably at least 70%, more preferably at least 80%, more preferably at least 85%, more preferably at least 90% or 95% of the heregulin expression level of BXPC3 or MCF7 cells.

46. A use or antibody for use according to any one of claims 31 to 45, wherein said subject has an ErbB-2 or ErbB-2/ErbB-3 positive tumor that has less than 1,000,000 ErbB-2 cell-surface receptors per cell.

47. A use or antibody for use according to any one of claims 31 to 46, wherein said antibody is an antibody according to any one of claims 1-29.

48. A use or antibody for use according to any one of claims 31 to 47, wherein said tumor cell is a breast cancer, gastric cancer, colorectal cancer, colon cancer, gastro-esophageal cancer, esophageal cancer, endometrial cancer, ovarian cancer, liver cancer, lung cancer including non-small cell lung cancer, clear cell sarcoma, salivary gland cancer, head and neck cancer, brain cancer, bladder cancer, pancreatic cancer, prostate cancer, kidney cancer, skin cancer, or melanoma cell.

49. A use or antibody for use according to any one of claims 31 to 48, wherein said subject has a cardiac function that is lower than 90% as compared to a healthy cardiac function.

50. A use or antibody for use according to claim 34 or 49, wherein said cardiac function comprises the Left Ventricular Ejection Fraction (LVEF).

51. A use or antibody for use according to claim 34 or 49 or 50, wherein said subject suffers from congestive heart failure (CHF), left ventricular dysfunction (LVD) and/or a $\geq$ 10% decreased Left Ventricular Ejection Fraction (LVEF), and/or wherein said subject has had a myocardial infarction.

52. An antibody according to any one of claims 1-29 for use in *in vivo* counteracting, preferably inhibiting, phosphorylation of Akt, ERK and/or S6 ribosomal protein.

53. Use of an antibody according to any one of claims 1-29 *in vitro* for counteracting, preferably inhibiting, phosphorylation of Akt, ERK and/or S6 ribosomal protein.