

MF2971); MF2971; MF3025; MF2916; MF3991 (is humanized MF3004); MF3031; MF2889; MF2913; MF1847; MF3001; MF3003 or MF1898 as depicted in Figure 16A or Figure 16E. Said second antigen-binding site is preferably present in a variable domain comprising a VH chain with the amino acid sequence of VH chain 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 as depicted in Figure 16B or Figure 16E or Figure 37. The immunoglobulin light chain in the variable domain preferably comprises the amino acid sequence of figure 16C.

An antibody of the invention is, unless otherwise specifically specified, preferably a bispecific antibody.

The invention further provides a pharmaceutical composition comprising an antibody according to the invention.

Further provided is an antibody according to the invention that further comprises a label, preferably a label for *in vivo* imaging.

The invention also provides a use of a bispecific antibody according to the invention in the manufacture of a medicament for the treatment of a subject having ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor or at risk of having said tumor. Also disclosed is a method 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 comprising administering to the subject a bispecific antibody according to the inventiondisclosure. Also provided is a bispecific antibody according to the invention 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.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a bispecific antibody comprising a first antigen-binding site that binds ErbB-2 and a second antigen-binding site that binds ErbB-3, wherein the bispecific antibody reduces or can reduce a ligand-induced receptor function of ErbB-3 on a ErbB-2 and ErbB-3 positive cell.

31. A bispecific antibody according to claim 30, wherein said compatible heterodimerization domains are compatible immunoglobulin heavy chain CH3 heterodimerization domains.

5 32. A bispecific antibody according to any one of claims 1-31, wherein both arms comprise a common light chain.

33. A bispecific antibody according to claim 32, wherein said common light chain is a germline light chain, preferably a rearranged germline human
10 kappa light chain comprising the IgVKI-39 gene segment, most preferably the rearranged germline human kappa light chain IgVKI-39*01/IGJKI*01.

34. A bispecific antibody according to any one of claims 1-33, further comprising a label, preferably a label for *in vivo* imaging.

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35. A pharmaceutical composition comprising a bispecific antibody according to any one of claims 1-34.

36. A method for the treatment of a subject having a ErbB-2, ErbB-3 or ErbB-
20 2/ErbB-3 positive tumor or at risk of having said tumor comprising administering to the subject an antibody or pharmaceutical composition according to any one of claims 1-35.

37. An antibody according to any one of claims 1-34, for use in the treatment of
25 a subject having or at risk of having an ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor.

38. An antibody for use according to claim 37, wherein said bispecific antibody does not significantly affect the survival of cardiomyocytes.

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39. An antibody for use according to claim 37 or 38, 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.

40. A method 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 comprising administering to the subject:

- a bispecific antibody comprising a first antigen-binding site that binds ErbB-2
5 and a second antigen-binding site that binds 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
10 PI3Ka inhibitor, an Akt inhibitor, an mTOR inhibitor, an Src inhibitor, vorinostat and paclitaxel.

41. A bispecific antibody comprising a first antigen-binding site that binds ErbB-2 and a second antigen-binding site that binds ErbB-3 for use in the
15 treatment of a ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor, wherein said treatment comprises administering said bispecific antibody 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, preferably administering said
20 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, to a subject having a ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor.

25 42. A method or antibody for use according to claim 40 or 41, wherein said tyrosine kinase inhibitor comprises afatinib, lapatinib and/or neratinib.

43. A method or antibody for use according to any one of claims 40-42, wherein said PI3K inhibitor is BYL719.

30 44. A method or antibody for use according to any one of claims 40-43, wherein said Akt inhibitor is MK-2206.

45. A method or antibody for use according to any one of claims 40-44, wherein said mTOR inhibitor is everolimus.

46. A method or antibody for use according to any one of claims 40-45, wherein
5 said Src inhibitor is saracatinib.

47. A method or antibody for use according to any one of claims 40-46, wherein said microtubuli targeting drug is Paclitaxel.

10 48. A method or antibody for use according to any one of claims 40-47, wherein said HDAC inhibitor is vorinostat.

49. A method 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,
15 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, comprising administering to the subject a bispecific antibody comprising a first antigen-binding site that binds ErbB-2 and a
20 second antigen-binding site that binds ErbB-3.

50. A bispecific antibody comprising a first antigen-binding site that binds ErbB-2 and a second antigen-binding site that binds ErbB-3 for use in the treatment or prevention of the formation of a metastasis of a ErbB-2, ErbB-3 or
25 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.

30 51. A method or antibody for use according to any one of claims 36-50, 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.

52. A method or antibody for use according to any one of claims 36-51, wherein said antibody is an antibody according to any one of claims 1-34.

53. A method or antibody for use according to any one of claims 36-52, wherein
5 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.

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54. A method or antibody for use according to any one of claims 36-53, wherein said subject has a cardiac function that is lower than 90% as compared to a healthy cardiac function.

15 55. A method or antibody for use according to claim 39 or 54, wherein said cardiac function comprises the Left Ventricular Ejection Fraction (LVEF).

56. A method or antibody for use according to claim 39 or 54-55, wherein said
subject suffers from congestive heart failure (CHF), left ventricular dysfunction
20 (LVD) and/or a $\geq 10\%$ decreased Left Ventricular Ejection Fraction (LVEF), and/or wherein said subject has had a myocardial infarction.

57. Use of an antibody according to any one of claims 1-34 for counteracting, preferably inhibiting, phosphorylation of Akt, ERK and/or S6 ribosomal protein.

31. A bispecific antibody according to claim 30, wherein said compatible heterodimerization domains are compatible immunoglobulin heavy chain CH3 heterodimerization domains.
- 5 32. A bispecific antibody according to any one of claims 1-31, wherein both arms comprise a common light chain.
33. A bispecific antibody according to claim 32, wherein said common light chain is a germline light chain, preferably a rearranged germline human
10 kappa light chain comprising the IgVK1-39 gene segment, most preferably the rearranged germline human kappa light chain IgVK1-39*01/IGJK1*01.
34. A bispecific antibody according to any one of claims 1-33, further comprising a label, preferably a label for *in vivo* imaging.
- 15 35. A pharmaceutical composition comprising a bispecific antibody according to any one of claims 1-34.
36. Use of an antibody or pharmaceutical composition according to any one of
20 claims 1-35 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.
37. An antibody according to any one of claims 1-34, for use in the treatment of a
25 subject having or at risk of having an ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor.
38. An antibody for use according to claim 37, wherein said bispecific antibody does not significantly affect the survival of cardiomyocytes.
- 30 39. An antibody for use according to claim 37 or 38, 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.

40. Use of a bispecific antibody comprising a first antigen-binding site that binds ErbB-2 and a second antigen-binding site that binds 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
5 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
10 tumor.

41. A bispecific antibody comprising a first antigen-binding site that binds ErbB-2 and a second antigen-binding site that binds ErbB-3 for use in the treatment of a ErbB-2, ErbB-3 or ErbB-2/ErbB-3 positive tumor, wherein said
15 bispecific antibody 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, preferably administering said bispecific antibody and at least one compound selected from the group consisting of a tyrosine kinase inhibitor, a PI3Ka inhibitor,
20 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.

42. A use or antibody for use according to claim 40 or 41, wherein said tyrosine
25 kinase inhibitor comprises afatinib, lapatinib and/or neratinib.

43. A use or antibody for use according to any one of claims 40-42, wherein said PI3K inhibitor is BYL719.

30 44. A use or antibody for use according to any one of claims 40-43, wherein said Akt inhibitor is MK-2206.

45. A use or antibody for use according to any one of claims 40-44, wherein said mTOR inhibitor is everolimus.

46. A use or antibody for use according to any one of claims 40-45, wherein said Src inhibitor is saracatinib.
47. A use or antibody for use according to any one of claims 40-46, wherein said
5 microtubuli targeting drug is Paclitaxel.
48. A use or antibody for use according to any one of claims 40-47, wherein said HDAC inhibitor is vorinostat.
- 10 49. Use of a bispecific antibody comprising a first antigen-binding site that binds ErbB-2 and a second antigen-binding site that binds 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
15 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.
- 20 50. A bispecific antibody comprising a first antigen-binding site that binds ErbB-2 and a second antigen-binding site that binds 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
25 preferably at least 90% or 95% of the heregulin expression level of BXPC3 or MCF7 cells.
51. A use or antibody for use according to any one of claims 36-50, wherein said subject has an ErbB-2 or ErbB-2/ErbB-3 positive tumor that has less than
30 1.000.000 ErbB-2 cell-surface receptors per cell.
52. A use or antibody for use according to any one of claims 36-51, wherein said antibody is an antibody according to any one of claims 1-34.

53. A use or antibody for use according to any one of claims 36-52, 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,
5 salivary gland cancer, head and neck cancer, brain cancer, bladder cancer, pancreatic cancer, prostate cancer, kidney cancer, skin cancer, or melanoma cell.
54. A use or antibody for use according to any one of claims 36-53, wherein said
10 subject has a cardiac function that is lower than 90% as compared to a healthy cardiac function.
55. A use or antibody for use according to claim 39 or 54, wherein said cardiac function comprises the Left Ventricular Ejection Fraction (LVEF).
- 15 56. A use or antibody for use according to claim 39 or 54-55, 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.
- 20 57. An antibody according to any one of claims 1-34 for use in counteracting, preferably inhibiting, phosphorylation of Akt, ERK and/or S6 ribosomal protein.