

others, signaling from other HER family of receptors and compensatory signaling from RTKs outside of the HER family (Thery et al., Resistance to human epidermal growth factor receptor type 2-targeted therapies, *Eur J Cancer* (2014), Vol. 50, Issue 5, pages 892-901 (<http://dx.doi.org/10.1016/j.ejca.2014.01.003>)). For example, overexpression of HER3 or its ligands along with HER2 leads to the formation of HER-2/HER-3 heterodimers and acquired resistance to trastuzumab. Thus, the antibody trastuzumab is thought to be ineffective in blocking signaling driven by ErbB-3 ligands (Wehrman, Raab et al. 2006, Junttila, Akita et al. 2009, Thery et al. 2014).

Recently the monoclonal antibody pertuzumab was approved for use in combination with trastuzumab on the basis of an extra 5 months progression-free survival benefit (Baselga, Cortes et al. 2012). Pertuzumab also binds ErbB-2 but at a different position than trastuzumab.

Other strategies to treat ErbB-2 positive tumors are directed towards ErbB-3. ErbB-3 binding monoclonal antibodies have demonstrated activity in preclinical studies (Schoeberl, Faber et al. 2010). Some ErbB-3 binding monoclonal antibodies can inhibit proliferation and growth of a variety of cancers.

Another strategy involves binding of both the ErbB-2 and ErbB-3 receptor. The molecule MM-111, is an artificial biological molecule containing two single chain Fv (scFv) fragments that bind ErbB-2 and ErbB-3. The two scFv are associated with a mutated human serum albumin (HSA) protein to increase the half-life of the molecule. In preclinical testing the molecule was shown to inhibit ErbB-3 signaling and proliferation. This effect was predominantly measured on ErbB-3 positive cell lines that expressed relatively high amounts of ErbB-2.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides 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.

In another aspect, the present invention provides 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.

In yet another aspect, the present invention provides 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.

In yet another aspect, the present invention provides a pharmaceutical composition comprising a bispecific antibody disclosed herein.

In yet another aspect, the present invention provides use of an antibody or pharmaceutical composition disclosed herein 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.

In yet another aspect, the present invention provides an antibody disclosed herein, 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.

In yet another aspect, the present invention provides 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.

In yet another aspect, the present invention provides 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
5 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,
10 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.

In yet another aspect, the present invention provides 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
15 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
20 expression level of BXPC3 or MCF7 cells.

In yet another aspect, the present invention provides 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
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 In yet another aspect, the present invention provides an antibody as disclosed herein for use in therapy or as a medicament.

In yet another aspect, the present invention provides use of an antibody disclosed herein *in vitro* for counteracting, preferably inhibiting, phosphorylation of Akt, ERK and/or S6 ribosomal protein.

5 The disclosure provides a bispecific antibody comprising a first antigen-binding site that binds ErbB-2 and a second antigen-binding site that binds ErbB-3, and wherein the antibody can reduce a ligand-induced receptor function of ErbB-3 on a ErbB-2 and ErbB-3 positive cell. Said first antigen-binding site is preferably present in a variable domain comprising a VH chain with the amino acid sequence of VH chain MF2926; MF2930; MF1849; MF2973; MF3004; MF3958 (is humanized

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;
 5 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.

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

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

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

20 The disclosure also provides a use of a bispecific antibody according to the
 disclosure 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
 25 the subject a bispecific antibody according to the disclosure. Also provided is a
 bispecific antibody according to the disclosure 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

30 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.

8. A bispecific antibody according to claim 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
5 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
10 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
15 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
20 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
25 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.
- 30 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-

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
5 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 PI3Ka inhibitor is BYL719.

10 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.

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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
20 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.

25 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
30 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.

52. An antibody according to any one of claims 1-29 for use in therapy or as a medicament.
- 5 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.