

### Claims

1. A bispecific antibody comprising a first antigen-binding site that binds EGFR and a second antigen-binding site that binds ErbB-3, wherein the antibody has a half maximal growth inhibitory concentration (IC<sub>50</sub>) of less than 200 pM for inhibiting EGFR and ErbB-3 ligand induced growth of BxPC3 cells (ATCC CRL-1687) or BxPC3-luc2 cells (Perkin Elmer 125058).
2. A bispecific antibody according to claim 1, that has an IC<sub>50</sub> for inhibiting EGFR and ErbB-3 ligand induced growth of BxPC3 cells (ATCC CRL 1687) or BxPC3-luc2 cells (Perkin Elmer 125058) of less than 100 pM, preferably less than 50 pM, more preferably less than 20 pM.
3. A bispecific antibody according to claim 1 or claim 2, wherein said first antigen-binding site binds domain I or domain III of EGFR.
4. A bispecific antibody according to any one of claims 1-3, that can reduce a ligand-induced receptor function of ErbB-3 on an EGFR and ErbB-3 positive cell.
5. A bispecific antibody according to any one of claims 1-4, wherein said ligand induced BxPC3 cells are EGFR and ErbB-3 ligand induced BxPC3 cells.
6. A bispecific antibody according to any one of claims 1-5, wherein said ligand comprises EGF, neuregulin1 or a combination thereof.
7. A bispecific antibody according to any one of claims 1-6, comprising a first antigen-binding site that binds EGFR and a second antigen-binding site that binds ErbB-3, wherein said second antigen-binding site binds domain III of ErbB-3.
8. A bispecific antibody according to any one of claims 1-7, wherein the antibody can reduce ligand-induced growth of an EGFR and ErbB-3 positive cell.

9. A bispecific antibody according to any one of claims 1-8, 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.
10. An antibody according to any one of claims 1-9, 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.
11. An antibody according to any one of claims 1-10, comprising an amino acid sequence of SEQ ID NO: 6-152.
12. An antibody according to any one of claims 1-11, 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 (SEQ ID NO: 88), MF3176 (SEQ ID NO: 93), MF3163 (SEQ ID NO: 98), MF3307 (SEQ ID NO: 108), MF6055 (SEQ ID NO: 113), MF6056 (SEQ ID NO: 115), MF6057 (SEQ ID NO: 117), MF6058 (SEQ ID NO: 119), MF6059 (SEQ ID NO: 121), MF6060 (SEQ ID NO: 123), MF6061 (SEQ ID NO: 125), MF6062 (SEQ ID NO: 127), MF6063 (SEQ ID NO: 129), MF6064 (SEQ ID NO: 131), MF6065 (SEQ ID NO: 133), MF6066 (SEQ ID NO: 135), MF6067 (SEQ ID NO: 137), MF6068 (SEQ ID NO: 139), MF6069 (SEQ ID NO: 141), MF6070 (SEQ ID NO: 143), MF6071 (SEQ ID NO: 145), MF6072 (SEQ ID NO: 147), MF6073 (SEQ ID NO: 149) and MF6074 (SEQ ID NO: 151).
13. A bispecific antibody according to claims 1-12, which exhibits antibody-dependent cell-mediated cytotoxicity (ADCC).
14. A bispecific antibody according to any one of claims 1-13, which is afucosylated in order to enhance ADCC.
15. A bispecific antibody according to any one of claims 1-14, that is a human or humanized antibody.

16. A bispecific antibody according to any one of claims 1-15, comprising two different immunoglobulin heavy chains with compatible hetero-dimerization domains.
17. A bispecific antibody according to claim 16, wherein said compatible hetero-dimerization domains are compatible immunoglobulin heavy chain CH3 hetero-dimerization domains.
18. A bispecific antibody according to claim 16 or claim 17, comprising two different immunoglobulin light chains with compatible hetero-dimerization domains.
19. A bispecific antibody according to any one of claims 1-18, comprising a common light chain, the light chain preferably comprises a light chain variable region IGKV1-39, preferably a germ-line IGKV1-39 variable region.
20. A pharmaceutical composition comprising a bispecific antibody according to any one of claims 1-19.
21. A bispecific antibody according to any one of claims 1-20, further comprising a label, preferably a label for in vivo imaging.
22. The use of a bispecific antibody according to any one of claims 1-21 in the manufacture of a medicament for the treatment of a subject having a EGFR, ErbB-3 or EGFR/ErbB-3 positive tumor or at risk of having said tumor.
23. A bispecific antibody according to any one of claims 1-21, for use in the treatment of a subject having or at risk of having an EGFR, ErbB-3 or EGFR/ErbB-3 positive tumor.
24. A bispecific antibody according to any one of claims 1-21 and 23, wherein said bispecific antibody induces less skin toxicity by producing less proinflammatory chemokines, preferably CXCL14, and inducing less impairment of antimicrobial RNAses, preferably Rnase 7 as compared to cetuximab under otherwise similar conditions.

25. The use of a bispecific antibody comprising a first antigen-binding site that binds EGFR 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 EGFR, ErbB-3 or EGFR/ErbB-3 positive tumor, wherein said EGFR, ErbB-3 or EGFR/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 BXP3 or MCF7 cells.

26. A bispecific antibody comprising a first antigen-binding site that binds EGFR 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 EGFR, ErbB-3 or EGFR /ErbB-3 positive tumor cell, wherein said EGFR, ErbB-3 or EGFR /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 BXP3 or MCF7 cells.

27. A use or antibody for use according to any one of claims 22-26, wherein said subject has an EGFR or EGFR/ErbB-3 positive tumor that has less than 1,000,000 ErbB-2 cell-surface receptors per cell.

28. A use or antibody for use according to any one of claims 22-27, wherein said bispecific antibody is an antibody according to any one of claims 1-21 or 23.

29. A use or antibody for use according to any one of claims 22-28, wherein said tumor cell is a breast cancer cell, an ovarian cancer cell, a gastric cancer cell, a colorectal cancer cell, a pancreatic cancer cell or a lung cancer cell.