

Also provided is an antibody of the invention that further comprises a label, preferably a label for in vivo imaging.

5 The invention further provides a bispecific antibody as described herein,
comprising two different immunoglobulin light chains with compatible hetero-
dimerization domains. Also disclosed is a method for the treatment of a subject having
a EGFR, ErbB-3 or EGFR/ErbB-3 positive tumor or at risk of having said tumor
comprising administering to the subject a bispecific antibody according to the
10 invention. 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 EGFR, ErbB-3 or EGFR/ErbB-
3 positive tumor.

DETAILED DESCRIPTION OF THE INVENTION

15 As used herein, the term "antigen-binding site" refers to a site on an antibody
which is capable of binding to antigen. The unmodified antigen-binding site is typically
formed by and present in the variable domain of the antibody. In one embodiment an
antibody variable domain of the invention comprises a heavy chain variable region
20 (VH) and a light chain variable region (VL). The antigen-binding site can be present in
the combined VH/VL variable domain, or in only the VH region or only the VL region.
When the antigen-binding site is present in only one of the two regions of the variable
domain, the counterpart variable region can contribute to the folding and/or stability of
the binding variable region, but does not significantly contribute to the binding of the
25 antigen itself.

Antigen binding by an antibody is typically mediated through the
complementarity determining regions (CDR's) of the antibody and the specific three-
dimensional structure of both the antigen and the variable domain allowing these two
30 structures to bind together with precision (an interaction similar to a lock and key), as
opposed to random, non-specific sticking of antibodies. As an antibody typically recognizes
only part of an antigen (called the epitope), and as such epitope may be present in other,
but preferably non-human, compounds as well, antibodies according to the present
invention that bind EGFR and/or ErbB-3 may recognize other proteins as well, but
35 preferably not other human proteins, if such other compounds contain the same
epitope. Hence, the term "binding" does

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. ~~A method for the treatment of a subject having a EGFR, ErbB-3 or EGFR/ErbB-3 positive tumor or at risk of having said tumor comprising administering to the subject~~ 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 as compared to cetuximab.

25. ~~A method 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 BXPC3 or MCF7 cells, comprising administering to the subject~~ 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 BXPC3 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 BXPC3 or MCF7 cells.

27. A ~~method 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 ~~method 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 ~~method 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.