site is blocked for the other antigen. Therefore, MEHD7945A (called a 'two in one' antibody) can be regarded both as an EGFR-targeting antibody, as well as a HER3 targeting antibody.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a bispecific antibody comprising two different immunoglobulin heavy chains and 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 (IC50) 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).

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

In yet another aspect, the present invention provides the use of a bispecific antibody disclosed herein 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.

In yet another aspect, the present invention provides a bispecific antibody disclosed herein for use in the treatment of a subject having or at risk of having an EGFR, ErbB-3 or EGFR/ErbB-3 positive tumor.

In yet another aspect, the present invention provides 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.

In yet another aspect, the present invention provides 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.

The disclosure provides a bispecific antibody comprising a first antigen-binding site that binds EGFR and a second antigen-binding site that binds ErbB-3 and wherein the antibody has a half maximal growth inhibitory concentration (IC50) of less than 200 pM for inhibiting EGFR and/or ErbB-3 ligand induced growth of BxPC3 cells (ATCC CRL-1687) or BxPC3-luc2 cells (Perkin Elmer 125058).

Further provided is an antibody that comprises an antigen-binding site that binds EGFR, wherein the antibody comprises an immunoglobulin heavy chain with a heavy chain variable region that binds EGFR and that comprises the amino acid sequence of VH chain MF3998; MF4280; MF4002; MF4003; MF4010; MF4289; MF3370; MF3751; MF3752 as depicted in Figure 11A, preferably wherein the immunoglobulin light chain variable region comprises the amino acid sequence of Figure 11C

The disclosure further provides an antibody that comprises an antigen-binding site that binds ErbB-3, comprising an immunoglobulin heavy chain with a heavy chain variable region that binds ErbB-3 and that comprises the amino acid sequence of VH chain MF3178; MF3176; MF3163; MF3307, MF6055-MF6074, preferably MF3178, MF3176, MF3163, MF6058, MF6061 or MF6065 as depicted in Figure 11B, preferably wherein the immunoglobulin light chain variable region comprises the amino acid sequence of Figure 11C.

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

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

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

The disclosure 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 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 EGFR, ErbB-3 or EGFR/ErbB-3 positive tumor.

DETAILED DESCRIPTION OF THE INVENTION

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 (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 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 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 preferably not other human proteins, if such other compounds contain the same epitope. Hence, the term "binding" does

Claims

1. A bispecific antibody comprising two different immunoglobulin heavy chains and 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 (IC50) 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 IC50 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.