

Claims

1. Use of a bispecific antibody that comprises two heavy chain variable regions (VH), each of which is paired with the same light chain variable region (VL), comprising a first antigen-binding site that can bind domain I of ErbB-2 and a second antigen-binding site that can bind domain III of ErbB-3 in the manufacture of a medicament for the treatment of an individual that has an ErbB-2 and ErbB-3 positive cancer cell, wherein the individual has been screened to identify the ErbB-2 and ErbB-3 positive cancer cell to comprise an NRG1 fusion gene comprising at least a portion of the NRG1-gene fused to a sequence from a different chromosomal location.
2. The use of claim 1, wherein the NRG1 fusion gene comprises at least the 3' end of the NRG1-gene fused to a 5' sequence from a different chromosomal location.
3. The use of claim 1 or 2, wherein the cancer cell is associated with an NRG1-fusion.
4. The use of claim 3, wherein the cancer cell is driven by NRG1-fusion.
5. The use of any one of the preceding claims, wherein the cell is a breast cancer cell, an ovarian cancer cell, a lung cancer cell, such as non-small cell lung cancer, or a metastasis thereof.
6. Use of a bispecific antibody that comprises two heavy chain variable regions (VH), each of which is paired with the same light chain variable region (VL), comprising a first antigen-binding site that can bind domain I of ErbB-2 and a second antigen-binding site that can bind domain III of ErbB-3 in the manufacture of a medicament for the treatment of an individual that has an ErbB-2 and ErbB-3 positive tumor or is at risk of having said tumor, wherein the individual has been screened to identify a cell of the ErbB-2 and ErbB-3 positive tumor to express an NRG1 fusion gene comprising at least the 3' end of the NRG1-gene fused to a 5' sequence from a different chromosomal location.

7. The use of claim 6, wherein the tumor is breast cancer, an ovarian cancer, a lung cancer, such as non-small cell lung cancer, or a metastasis thereof.
8. The use of any one of the preceding claims, wherein the NRG1-fusion gene expresses a protein that comprises an NRG1 EGF-like domain.
9. The use of any one of the preceding claims, wherein the NRG-fusion is a fusion of NRG1 and a gene on human chromosome 8
10. The use of claim 9, wherein the gene on human chromosome 8 encodes an excreted protein or a cellular membrane associated protein.
11. The use of any one of the preceding claims, wherein the NRG1 fusion gene is a fusion of the 3' end of the NRG1-gene with the 5' sequence of one of the genes selected from the group consisting of CD74; DOC4; TNFRSF10B; CLU; VAMP2; SLC3A2; RBPMS; WRN; SDC4; KIF13B; SLECA2; PDE7A; ATP1B1; CDK1; BMPR1B; MCPH1 and RAB2IL1.
12. The use of any one of the preceding claims, wherein the cell or tumor is of an epithelial origin.
13. The use of any one of the preceding claims, wherein the individual has undergone a therapy targeted towards EGFR inhibition
14. The use of claim 13, wherein the individual has undergone a therapy with cetuximab.
15. The use of any one of the preceding claims, wherein the ErbB-1 cell-surface receptor density; ErbB-2 cell-surface receptor density; ErbB-3 cell-surface receptor density; ErbB-4 cell-surface receptor density or a combination thereof on the cell or cells of the tumor is determined.
16. The use of any one of the preceding claims, characterized in that the cell or tumor has less than 400,000 ErbB-1 cell-surface receptors per cell.

17. The use of any one of the preceding claims, further comprising administering to the individual an ErbB-1 inhibitor

18. The use of claim 17, wherein the ErbB-1 inhibitor is cetuximab.

19. The use of any one of the preceding claims, wherein the affinity of the first antigen-binding site for ErbB-2 is lower than the affinity of the second antigen-binding site for ErbB-3.

20. The use according to claim 19, wherein said antibody comprises:

- i) at least the CDR1, CDR2 and CDR3 sequences of an ErbB 2 specific heavy chain variable region selected from the group consisting of MF2926, MF2930, MF1849; MF2973, MF3004, MF3958, MF2971, MF3025, MF2916, MF3991, MF3031, MF2889, MF2913, MF1847, MF3001, MF3003 and MF1898; and
- ii) at least the CDR1, CDR2 and CDR3 sequences of an ErbB 3 specific heavy chain variable region selected from the group consisting of MF3178; MF3176; MF3163; MF3099; MF3307; MF6055; MF6056; MF6057; MF6058; MF6059; MF6060; MF6061; MF6062; MF6063; MF6064; MF6065; MF6066; MF6067; MF6068; MF6069; MF6070; MF6071; MF6072; MF6073 and MF6074, and

at least a light chain variable region comprising a CDR1 sequence comprising RASQSISSYLN, a CDR2 sequence comprising AASSLQS, and a CDR3 sequence comprising QQSYSTPPT.

21. The use according to claim 20, wherein said antibody comprises

- a) an ErbB 2 specific heavy chain variable region sequence selected from the group consisting of the heavy chain variable region sequences of MF2926, MF2930, MF1849; MF2973, MF3004, MF3958, MF2971, MF3025, MF2916, MF3991, MF3031, MF2889, MF2913, MF1847, MF3001, MF3003 and MF1898; and
- b) an ErbB 3 specific heavy chain variable region sequence selected from the group consisting of the heavy chain variable region sequences of 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 and MF6074, and

at least a light chain variable region comprising a CDR1 sequence comprising RASQSISSYLN, a CDR2 sequence comprising AASSLQS, and a CDR3 sequence comprising QQSYSTPPT.

22. The use of claim 20 or 21, wherein the antibody comprises at least the CDR1, CDR2 and CDR3 sequences of the ErbB 2 specific heavy chain variable region MF3958 and at least a light chain variable region comprising a CDR1 sequence comprising RASQSISSYLN, a CDR2 sequence comprising AASSLQS, and a CDR3 sequence comprising QQSYSTPPT; and the antibody comprises at least the CDR1, CDR2 and CDR3 sequences of the ErbB 3 specific heavy chain variable region MF3178 and at least a light chain variable region comprising a CDR1 sequence comprising RASQSISSYLN, a CDR2 sequence comprising AASSLQS, and a CDR3 sequence comprising QQSYSTPPT.

23. The use of any one of claims 20 to 22, wherein the variable domain that comprises said first antigen binding site and the variable domain that comprises said second antigen binding site comprise the same light chain variable region comprising a human germline sequence having at least a CDR1 sequence comprising RASQSISSYLN, a CDR2 sequence comprising AASSLQS, and a CDR3 sequence comprising QQSYSTPPT.

24. The use of claim 23, wherein the variable domain that comprises said first antigen binding site and the variable domain that comprises said second antigen binding site comprise a germline light chain O12 light chain variable region.

25. The use of claim 23 or 24, wherein the variable domain that comprises said first antigen binding site and the variable domain that comprises said second antigen binding site comprise a common light chain variable region comprising a rearranged human kappa light chain IgVKl-39*01/IGJKl*01.