

Claims

1. Use of an ErbB-2/ErbB-3 bispecific antibody and a therapeutically effective amount of an endocrine therapy drug in the manufacture of a medicament for treating a subject that has hormone receptor positive breast cancer or is at risk of having said cancer, wherein the bispecific antibody comprises two heavy chain variable regions (VH), each of which is paired with a huVκ1-39 light chain variable region (VL), wherein one VH has an antigen-binding site that can bind domain I of ErbB-2 comprising at least the CDR1, CDR2 and CDR3 sequences selected from the group consisting of MF2973, MF3004, MF3958, MF2971, MF3025, MF2916, MF3991, MF3031 and MF3003; and the other VH has an antigen-binding site that can bind domain III of ErbB-3 comprising at least the CDR1, CDR2 and CDR3 sequences selected from the group consisting of MF3178; MF3176; MF3163; MF6055; MF6056; MF6057; MF6058; MF6059; MF6060; MF6061; MF6062; MF6063; MF6064; MF6065; MF6066; MF6067; MF6068; MF6069; MF6070; MF6071; MF6072; MF6073 and MF6074.

2. The use of claim 1, wherein the affinity of the antigen-binding site for ErbB-3 is equal to or higher than the affinity of the antigen-binding site for ErbB-2.

3. The use according to claim 1 or 2, wherein the huVκ1-39 light chain comprises the sequence
DIQMTQSPSSLSASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVP
SRFSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPPTFGQGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS
STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC, or with 1-5 amino acid
insertions, deletions, substitutions or a combination thereof.

4. The use according to any one of claims 1-3, wherein one VH comprises CDR1, CDR2 and CDR3 sequences AYYIN, RIYPGSGYTSYAQKFQG and PPVYYDSAWFAY, respectively, of an ErbB-2 specific heavy chain variable region.

5. The use according to any one of claims 1-4, wherein one VH comprises CDR1, CDR2 and CDR3 sequences GYYMH, WINPNSGGTNYAQKFQG and DHGSRHFWSYWGFYDY, respectively, of an ErbB-3 specific heavy chain variable region.

6. The use according to any one of claims 1-5, wherein the endocrine therapy drug comprises an aromatase inhibitor; a selective estrogen receptor modulator (SERM); or a selective estrogen receptor downregulator (SERD).
7. The use according to any one of claims 1-6, wherein the endocrine therapy drug comprises a selective estrogen receptor modulator (SERM) selected from the group consisting of Tamoxifen (Nolvadex), broparestrol (Acnestrol), cyclofenil (Sexovid), raloxifene (Evista) and toremifene (Fareston).
8. The use according to any one of claims 1-7, wherein the endocrine therapy drug comprises Tamoxifen.
9. The use according to any one of claims 1-6, wherein the endocrine therapy drug comprises Fulvestrant.
10. The use according to any one of claims 1-6, wherein the endocrine therapy drug comprises Letrozole.
11. The use according to any one of claims 1-10, wherein the breast cancer is an estrogen receptor positive breast cancer.
12. The use according to any one of claims 1-11, wherein the breast cancer is a progesterone receptor positive breast cancer.
13. The use according to any one of claims 1-12, wherein the breast cancer is an immunohistochemistry ErbB-2 + cancer or an immunohistochemistry ErbB-2 ++ without ErbB-2 gene amplification cancer.
14. The use according to any one of claims 1-13, wherein the breast cancer is ER positive with low HER2 expression metastatic breast cancer immunohistochemistry (IHC) 1+, or IHC 2+, combined with negative FISH.
15. The use according to any one of claims 1-14, wherein the subject had received, is receiving, or will receive a cyclin dependent kinase 4/6 inhibitor.

16. The use according to any one of claims 1-15, wherein the subject had received one or more endocrine therapy treatments prior to initiation of a treatment with said ErbB-2/ErbB-3 bispecific antibody and said therapeutically effective amount of an endocrine therapy drug.

17. The use according to any one of claims 1-16, wherein the subject had received a cyclin-dependent kinase inhibitor prior to initiation of a treatment with said ErbB-2/ErbB-3 bispecific antibody and said therapeutically effective amount of an endocrine therapy drug.

18. The use according to any one of claims 1-17, wherein the expression level of an estrogen receptor, ErbB-2, ErbB-3, or a combination thereof on cells of said cancer has been determined.

19. The use according to any one of claims 1-18, wherein the subject has a hormone receptor positive status (estrogen receptor positive [ER+] and/or progesterone receptor positive [PR+]), for $\geq 1\%$ positive cells as determined by immunohistochemistry on a tumor biopsy.

20. The use according to any one of claims 1-19, wherein said bispecific antibody comprises a variable domain with a heavy chain variable region comprising the ErbB-2 specific heavy chain variable region of MF3958 and a variable domain with a heavy chain variable region comprising the ErbB-3 specific heavy chain variable region of MF3178.

21. The use according to any one of claims 1-20, wherein the ErbB-2/ErbB-3 bispecific antibody is to be administered as an intravenous dose of 300mg to 900mg.

22. The use according to claim 21, wherein the bispecific antibody is to be administered every two to four weeks.

23. The use according to any one of claims 1-22, wherein the ErbB-2 specific heavy chain variable region comprises the sequence
QVQLVQSGAEVKKPGASVKLSCKASGYTFTAYYINWVRQAPGQGLEWIGRIYPGSGY

TSYAQKFQGRATLTADDESTSTAYMELSSLRSED TAVYFCARPPVYYDSAWFAYWGQG
TLVTVSS.

24. The use according to any one of claims 1-23, wherein the ErbB-3 specific heavy chain variable region comprises the sequence

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPNS
GGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARDHGSRHFWSYWG
FDYWGQGTLVTVSS.

25. The use according to any one of claims 1-24, wherein the huV κ 1-39 light chain comprises the sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPTFGQGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS
STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC.