

Claims

1. A 4-1BBL trimer-containing antigen binding molecule comprising
 - (a) an antigen binding domain capable of specific binding to Her2,
 - (b) a first and a second polypeptide that are linked to each other by a disulfide bond,
- 5 wherein the antigen binding molecule is characterized in that the first polypeptide comprises two ectodomains of 4-1BBL or a fragment thereof that are connected to each other by a peptide linker and in that the second polypeptide comprises one ectodomain of 4-1BBL or a fragment thereof, and
- (c) an Fc domain composed of a first and a second subunit capable of stable association.
- 10 2. The 4-1BBL trimer-containing antigen binding molecule of claim 1, wherein the ectodomain of 4-1BBL or a fragment thereof comprises the amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO: 2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO: 6, SEQ ID NO:7 and SEQ ID NO:8, particularly the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:5.
- 15 3. The 4-1BBL trimer-containing antigen binding molecule of claims 1 or 2, comprising
 - (a) an antigen binding domain capable of specific binding to Her2,
 - (b) a first and a second polypeptide that are linked to each other by a disulfide bond,
- 20 wherein the antigen binding molecule is characterized in that the first polypeptide comprises the amino acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11 and SEQ ID NO:12 and in that the second polypeptide comprises the amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:5, SEQ ID NO:3 and SEQ ID NO:4, and
- (c) an Fc domain composed of a first and a second subunit capable of stable association.
4. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 3,
- 25 wherein the Fc domain comprises knob-into-hole modifications promoting association of the first and the second subunit of the Fc domain.
5. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 4, wherein the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor, in particular towards Fcγ receptor.
- 30 6. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 5, wherein the Fc domain is an IgG1 Fc domain comprising the amino acid substitutions the amino acid substitutions L234A, L235A and P329G (numbering according to Kabat EU index).

7. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 6, wherein the antigen binding domain capable of specific binding to Her2 is a Fab molecule capable of specific binding to Her2.
8. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 7, wherein the antigen binding domain capable of specific binding to Her2 comprises
(a) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:13, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:14, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:15, and a VL domain comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:16, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:17, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:18, or
(b) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:21, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:22, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:23, and a VL domain comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:24, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:25, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:26, or
(c) a VH domain comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:29, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:30, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:31, and a VL domain comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:32, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:33, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:34.
9. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 9, wherein the antigen binding domain capable of specific binding to Her2 comprises
(a) a VH domain comprising an amino acid sequence of SEQ ID NO:19 and a VL domain comprising an amino acid sequence of SEQ ID NO:20, or
(b) a VH domain comprising an amino acid sequence of SEQ ID NO:27 and a VL domain comprising an amino acid sequence of SEQ ID NO:28, or
(c) a VH domain comprising an amino acid sequence of SEQ ID NO:35 and a VL domain comprising an amino acid sequence of SEQ ID NO:36.
10. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 9, wherein the antigen binding molecule comprises a first heavy chain and a first light chain, both comprising a Fab molecule capable of specific binding to Her2,

a second heavy chain comprising the constant domains and two ectodomains of a 4-1BBL or a fragment thereof connected to each other by a first peptide linker fused at its C-terminus by a second peptide linker to a second heavy or light chain,
and a second light chain comprising a constant domain and one ectodomain of said 4-1BBL
5 or a fragment thereof fused at its C-terminus by a third peptide linker to a second light or heavy chain, respectively.

11. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 10,
wherein the first peptide comprising two ectodomains of 4-1BBL or a fragment thereof
connected to each other by a first peptide linker is fused at its C-terminus by a second
10 peptide linker to a CL domain that is part of a heavy chain,
and the second peptide comprising one ectodomain of said 4-1BBL or a fragment thereof is
fused at its C-terminus by a third peptide linker to a CH1 domain that is part of a light chain.
12. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 11,
wherein the antigen binding molecule comprises
15 (i) a first heavy chain comprising the VH domain comprising the amino acid sequence of
SEQ ID NO:19 and a first light chain comprising the VL domain comprising the amino acid
sequence of SEQ ID NO:20 or
a first heavy chain comprising the VH domain comprising the amino acid sequence of SEQ
ID NO:27 and a first light chain comprising the VL domain comprising the amino acid
20 sequence of SEQ ID NO:28, or
a first heavy chain comprising the VH domain comprising the amino acid sequence of SEQ
ID NO:35 and a first light chain comprising the VL domain comprising the amino acid
sequence of SEQ ID NO:36,
(ii) a second heavy chain comprising the amino acid sequence selected from the group
consisting of SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41 and SEQ ID NO:43, and
25 (iii) a second light chain comprising the amino acid sequence selected from the group
consisting of SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42 and SEQ ID NO:44.
13. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 12,
wherein the antigen binding molecule comprises
30 (a) a first heavy chain comprising the amino acid sequence of SEQ ID NO:45, a first light
chain comprising the amino acid sequence of SEQ ID NO:46, a second heavy chain
comprising the amino acid sequence of SEQ ID NO:37 and a second light chain comprising
the amino acid sequence of SEQ ID NO:38, or
(b) a first heavy chain comprising the amino acid sequence of SEQ ID NO:47, a first light
35 chain comprising the amino acid sequence of SEQ ID NO:48, a second heavy chain

- comprising the amino acid sequence of SEQ ID NO:37 and a second light chain comprising the amino acid sequence of SEQ ID NO:38, or
- (c) a first heavy chain comprising the amino acid sequence of SEQ ID NO:49, a first light chain comprising the amino acid sequence of SEQ ID NO:50, a second heavy chain
- 5 comprising the amino acid sequence of SEQ ID NO:37 and a second light chain comprising the amino acid sequence of SEQ ID NO:38.
14. Isolated nucleic acid molecule encoding the 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 13.
15. A vector, particularly an expression vector, comprising the isolated nucleic acid molecule of
- 10 claim 14.
16. A host cell comprising the nucleic acid of claim 14 or the vector of claim 15.
17. A method of producing the 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 13, comprising culturing the host cell of claim 16 under conditions suitable for expression of the 4-1BBL trimer-containing antigen binding molecule.
- 15 18. The method of claim 17, further comprising recovering the antibody from the host cell.
19. A 4-1BBL trimer-containing antigen binding molecule produced by the method of claim 18.
20. A pharmaceutical composition comprising the 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 13 or 19 and at least one pharmaceutically acceptable excipient.
- 20 21. The pharmaceutical composition of claim 20, further comprising an additional therapeutic agent.
22. The pharmaceutical composition of claims 20 or 21, further comprising a T-cell activating anti-CD3 bispecific antibody.
23. The pharmaceutical composition of claim 22, wherein the T-cell activating anti-CD3
- 25 bispecific antibody is an anti-Her2/anti-CD3 bispecific antibody.
24. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 13, or the pharmaceutical composition of any one of claims 20 to 23, for use as a medicament.

25. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 13, or the pharmaceutical composition of any one of claims 20 to 23, for use in the treatment of cancer.
26. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 13, or the pharmaceutical composition of any one of claims 20 to 23, for use according to claim 25, wherein the 4-1BBL trimer-containing antigen binding molecule is used in combination with another therapeutic agent.
27. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 13 for use in the treatment of cancer, wherein the 4-1BBL trimer-containing antigen binding molecule is used in combination with a T-cell activating anti-CD3 bispecific antibody and wherein the T-cell activating anti-CD3 bispecific antibody is administered concurrently with, prior to, or subsequently to the 4-1BBL trimer-containing antigen binding molecule.
28. Use of the 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 13 for the manufacture of a medicament for the treatment of cancer.
29. Use of the 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 13 for the manufacture of a medicament for the treatment of cancer, wherein the 4-1BBL trimer-containing antigen binding molecule is used in combination with with a T-cell activating anti-CD3 bispecific antibody.
30. The use of claim 29, wherein the T-cell activating anti-CD3 bispecific antibody is an anti-Her2/anti-CD3 antibody.
31. A method of treating an individual having cancer comprising administering to the individual an effective amount of the 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 13, or the pharmaceutical composition of any one of claims 20 to 22.
32. A method for treating an individual having cancer comprising administering to the subject an effective amount of the 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 13, or the pharmaceutical composition of any one of claims 20 to 22 and an effective amount of a T-cell activating anti-CD3 bispecific antibody.
33. The method of claim 32, wherein the T-cell activating anti-CD3 bispecific antibody is an anti-Her2/anti-CD3 antibody.

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34. A method of up-regulating or prolonging cytotoxic T cell activity in an individual having cancer, comprising administering to the individual an effective amount of the 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 13, or the pharmaceutical composition of claim 20.