

2016/177802. These molecules are antibody-lipocalin mutein fusion polypeptides, meaning that a lipocalin mutein with binding specificity for CD137 is fused to an anti-Her2 antibody.

Lipocalin muteins (anticalins) are non-antibody scaffolds and the conversion of such modalities into differentiated drugs has been challenging (Vazquez-Lombardi et al. 2015, Drug Discovery

5 Today 20, 1271-1283). Compared to antibodies challenges could arise in view of different serum half-life, tissue penetration and immunogenicity. Thus, there is still a need for drug candidates with improved properties that are based on antibody technology or human-like proteins.

## SUMMARY

The new antigen binding molecules of the present disclosure combine an anti-Her2 antigen  
10 binding domain with a moiety that is capable of forming a costimulatory 4-1BBL trimer and that is sufficiently stable to be pharmaceutically useful. Surprisingly, antigen binding molecules of the disclosure provide a trimeric and thus biologically active human 4-1BB ligand, although one of the trimerizing 4-1BBL ectodomains is located on another polypeptide than the other two 4-1BBL ectodomains of the molecule. Targeted by the anti-Her2 antigen binding domain the  
15 antigen binding molecules of the present disclosure have an increased activity on the tumor site, comprise the natural human 4-1BB ligand and should thus impose less safety issues compared to conventional 4-1BB agonistic antibodies or more artificial fusion proteins.

In one aspect, the disclosure provides a 4-1BBL trimer-containing antigen binding molecule comprising

- 20 (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, 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  
25 thereof, and
- (c) an Fc domain composed of a first and a second subunit capable of stable association.

In a particular example, the disclosure provides a 4-1BBL trimer-containing antigen binding molecule, 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  
30 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.

In a further example, the disclosure provides a 4-1BBL trimer-containing antigen binding molecule, comprising

- (a) an antigen binding domain capable of specific binding to Her2,
- 35 (b) a first and a second polypeptide that are linked to each other by a disulfide bond,

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.

In one example, the Fc domain is an IgG, particularly an IgG1 Fc domain or an IgG4 Fc domain. More particularly, the Fc domain is an IgG1 Fc domain. In a particular example, the Fc domain comprises a modification promoting the association of the first and second subunit of the Fc domain. In a particular example, the disclosure provides a 4-1BBL trimer-containing antigen binding molecule, wherein the Fc domain comprises knob-into-hole modifications promoting association of the first and the second subunit of the Fc domain. In a specific example, the disclosure provides a 4-1BBL trimer-containing antigen binding molecule, wherein the first subunit of the Fc domain comprises the amino acid substitutions S354C and T366W (numbering according to Kabat EU index) and the second subunit of the Fc domain comprises the amino acid substitutions Y349C, T366S, L368A and Y407V (numbering according to Kabat EU index).

In another example, the disclosure is concerned with a 4-1BBL trimer-containing antigen binding molecule as defined herein before, comprising (c) an Fc domain composed of a first and a second subunit capable of stable association, wherein the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor, in particular towards Fc $\gamma$  receptor. In particular, the Fc domain comprises amino acid substitutions at positions 234 and 235 (EU numbering according to Kabat) and/or 329 (EU numbering according to Kabat) of the IgG heavy chains. Particularly, provided is a 4-1BBL trimer-containing antigen binding molecule, 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).

In one example, the 4-1BBL trimer-containing antigen binding molecule is one, wherein wherein the antigen binding domain capable of specific binding to Her2 is a Fab molecule capable of specific binding to Her2. In another example, the antigen binding domain capable of specific binding to Her2 is a cross-over Fab molecule or a scFV molecule capable of specific binding to Her2.

In one example, the disclosure provides a 4-1BBL trimer-containing antigen binding molecule as described herein before, wherein the 4-1BBL trimer-containing antigen binding molecule comprises one Fab domain capable of specific binding to Her2, meaning that it comprises monovalent binding towards Her2.

In a further example, provided is a 4-1BBL trimer-containing antigen binding molecule, wherein 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.

In a further example, the 4-1BBL trimer-containing antigen binding molecule of the disclosure 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.

In a further example, provided is a 4-1BBL trimer-containing antigen binding molecule, 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 4-1BBL or a fragment thereof fused at its C-terminus by a third peptide linker to a second light or heavy

chain, respectively. More particularly, provided is a 4-1BBL trimer-containing antigen binding molecule, 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 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.

In a particular example, the disclosure relates to a 4-1BBL trimer-containing antigen binding molecule as defined above, wherein the peptide linker is (G4S)<sub>2</sub>, i.e. a peptide linker of SEQ ID NO:68. In one example, the peptide linker in all instances is (G4S)<sub>2</sub>.

Provided is further a 4-1BBL trimer-containing antigen binding molecule, wherein in the CL domain adjacent to the TNF ligand family member the amino acid at position 123 (EU numbering) has been replaced by arginine (R) and the amino acid at position 124 (EU numbering) has been substituted by lysine (K), and wherein in the CH1 domain adjacent to the TNF ligand family member the amino acids at position 147 (EU numbering) and at position 213 (EU numbering) have been substituted by glutamic acid (E).

In another example, provided is a 4-1BBL trimer-containing antigen binding molecule, wherein the antigen binding molecule comprises

(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 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

(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.

In a particular example, provided is a 4-1BBL trimer-containing antigen binding molecule comprising

(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 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

5 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 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.

10 According to another aspect of the disclosure, there is provided an isolated nucleic acid molecule encoding a 4-1BBL trimer-containing antigen binding molecule as defined herein before. According to another aspect of the disclosure, there is provided a vector, particularly an expression vector, comprising the isolated nucleic acid molecule of the disclosure. According to another aspect of the disclosure, there is provided a host cell comprising the isolated nucleic acid  
15 or the vector of the disclosure. In some examples the host cell is an eukaryotic cell, particularly a mammalian cell.

There is also provided a method for producing the 4-1BBL trimer-containing antigen binding molecule of the disclosure, comprising culturing the host cell of the disclosure under conditions suitable for expression of the 4-1BBL trimer-containing antigen binding molecule, and isolating the 4-1BBL trimer-containing antigen binding molecule. In another aspect, there is  
20 provided a method of producing the 4-1BBL trimer-containing antigen binding molecule of the disclosure, comprising culturing the host cell of the disclosure under conditions suitable for expression of the 4-1BBL trimer-containing antigen binding molecule. In another aspect, there is provide a 4-1BBL trimer-containing antigen binding molecule produced by the method of the  
25 disclosure.

In another aspect, there is provided a pharmaceutical composition comprising the 4-1BBL trimer-containing antigen binding molecule of the disclosure and at least one pharmaceutically acceptable excipient. In another example, a pharmaceutical composition is provided comprising the 4-1BBL trimer-containing antigen binding molecule of the disclosure and at least one  
30 pharmaceutically acceptable excipient, further comprising an additional therapeutic agent, e.g. a chemotherapeutic agent and/ or other agents for use in cancer immunotherapy. In a further example, provided is a pharmaceutical composition further comprising a T-cell activating anti-CD3 bispecific antibody, in particular an anti-Her2/anti-CD3 bispecific antibody.

In another aspect, there is provided the 4-1BBL trimer-containing antigen binding molecule of the disclosure, or the pharmaceutical composition of the disclosure, for use as a medicament. In one example is provided the 4-1BBL trimer-containing antigen binding molecule of the disclosure, or the pharmaceutical composition of the disclosure, for use in the treatment of  
5 a disease in an individual in need thereof. In a specific example, provided is the 4-1BBL trimer-containing antigen binding molecule of the disclosure, or the pharmaceutical composition

of the disclosure, for use in the treatment of cancer. In another example, provided is the 4-1BBL trimer-containing antigen binding molecule of the disclosure, or the pharmaceutical composition of the disclosure, for use in up-regulating or prolonging cytotoxic T cell activity. In another aspect, there is provided the 4-1BBL trimer-containing antigen binding molecule of the disclosure, or the pharmaceutical composition of the disclosure, for use in the treatment of cancer or for up-regulating or prolonging cytotoxic T cell activity in an individual having cancer.

In another example, provided is the 4-1BBL trimer-containing antigen binding molecule of the disclosure, or the pharmaceutical composition of the disclosure, for use in the treatment of cancer, wherein the the 4-1BBL trimer-containing antigen binding molecule is used in combination with another therapeutic agent, in particular a T-cell activating anti-CD3 bispecific antibody. In one example, 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.

In another aspect, there is provided the 4-1BBL trimer-containing antigen binding molecule of the disclosure 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 to be administered concurrently with, prior to, or subsequently to the 4-1BBL trimer-containing antigen binding molecule.

Also provided is the use of the 4-1BBL trimer-containing antigen binding molecule of the disclosure for the manufacture of a medicament for the treatment of a disease in an individual in need thereof, in particular for the manufacture of a medicament for the treatment of cancer, as well as a method of treating a disease in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising the 4-1BBL trimer-containing antigen binding molecule as disclosed herein in a pharmaceutically acceptable form. In a specific example, the disease is cancer. In another aspect, there is provided use of the 4-1BBL trimer-containing antigen binding molecule of the disclosure in the manufacture of a medicament for the treatment of cancer. Further provided is the use of the 4-1BBL trimer-containing antigen binding molecule of the disclosure 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 a T-cell activating anti-CD3 bispecific antibody, in particular an anti-Her2/anti-CD3 antibody. In another aspect, there is provided use of the 4-1BBL trimer-containing antigen binding molecule of the disclosure in 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.

Furthermore, provided is 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 the disclosure, or a pharmaceutical composition thereof, and an effective amount of a T-cell activating anti-CD3 bispecific antibody, in particular an anti-Her2/anti-CD3 antibody. Also provided is 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 the disclosure, or the pharmaceutical composition of the disclosure. In any of the above examples the individual is preferably a mammal, particularly a human.

In another aspect, there is provided use of the 4-1BBL trimer-containing antigen binding molecule of the disclosure, or the pharmaceutical composition of the disclosure in the manufacture of a medicament for up-regulating or prolonging cytotoxic T cell activity in an individual having cancer.

## BRIEF DESCRIPTION OF THE DRAWINGS

**Figure 1** shows the components for the assembly of the monovalent Her2-targeting split trimeric 4-1BB ligand Fc fusion antigen binding molecules. **Fig. 1A** shows the dimeric 4-1BB ligand that is fused at the C-terminus to a human IgG1-CL domain with mutations E123R and Q124K (charged variant) and **Fig. 1B** shows the monomeric 4-1BB ligand fused at its C-terminus to a human IgG1-CH1 domain with mutations K147E and K213E (charged variant).

### Claims

1. A 4-1BBL trimer-containing antigen binding molecule comprising  
(a) an antigen binding domain capable of specific binding to Her2,  
5 (b) a first and a second polypeptide that are linked to each other by a disulfide bond,  
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  
10 fragment thereof, and  
(c) an Fc domain composed of a first and a second subunit capable of stable association.
2. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 5,  
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,  
15 particularly the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:5.
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,  
wherein the antigen binding molecule is characterized in that the first polypeptide comprises  
20 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.
- 25 4. The 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 3,  
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  
30 to an Fc receptor, in particular towards Fcγ receptor.
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,  
5 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  
or a fragment thereof fused at its C-terminus by a third peptide linker to a second light or  
10 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  
peptide linker to a CL domain that is part of a heavy chain,  
15 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  
(i) a first heavy chain comprising the VH domain comprising the amino acid sequence of  
20 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  
sequence of SEQ ID NO:28, or  
25 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  
30 (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  
(a) a first heavy chain comprising the amino acid sequence of SEQ ID NO:45, a first light  
35 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 chain comprising the amino acid sequence of SEQ ID NO:48, 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, 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

10 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 claim 14.

15 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.

18. The method of claim 17, further comprising recovering the antibody from the host cell.

20 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.

25 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 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.
- 5 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 or for up-regulating or prolonging cytotoxic T cell activity in an individual having cancer.
- 10 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.
- 15 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 to be 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 in the manufacture of a medicament for the treatment of cancer.
- 20 29. Use of the 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 13 in 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.
- 25 31. Use of the 4-1BBL trimer-containing antigen binding molecule of any one of claims 1 to 13, or the pharmaceutical composition of claim 20 in the manufacture of a medicament for up-regulating or prolonging cytotoxic T cell activity in an individual having cancer.