

cells and macrophages and NK-cells targeted to CEA expressing tumors offers a considerable opportunity for superior efficacy/killing and phagocytosis of CEA expressing tumor cells.

The so far disappointing results with CAR T-cells in solid tumors may have a simple explanation – the number of CAR T-cells penetrating the solid tumor and distributed in it are just not sufficient. This is certainly different in the majority of haematological malignancies; CAR T-cells can well access the tumor cells, explaining the difference of high efficacy in these malignancies compared to disappointing efficacy in solid tumors. In addition, CAR T-cells may be heavily suppressed by the tumor microenvironment (TME) of the solid tumors which is mostly strongly immune suppressive.

The present invention provides novel bispecific anti-CEAxCD3 antibodies with high efficacy, low influence of sCEA on efficacy, low or no crossreactivity to other CEACAM than CEACAM5 (= CEA) and therefore decreased toxicity, low immunogenicity, the opportunity of parallel combination therapy with CEAxCD47 antibodies and with valuable pharmacokinetic properties.

SUMMARY OF THE INVENTION

In one ~~embodiment~~example, the ~~invention relates~~disclosure refers to a bispecific antibody (further named also as “bsAb CEAxCD3” or “CEAxCD3 bispecific antibody”) comprising a first binding part, specifically binding to human CEACAM5 (further named also as “CEA”) and a second binding part, specifically binding to human CD3ε (further named also as “CD3”).

In one ~~embodiment~~example the bispecific antibody is characterized in that said antibody is monovalent for the first binding part and monovalent for the second binding part.

In one ~~example~~embodiment the bispecific antibody is characterized in that the constant and variable framework region sequences are human.

In one ~~example~~embodiment the bispecific antibody is characterized in that each of the first and second binding parts comprises an immunoglobulin heavy chain and an immunoglobulin light chain.

In one ~~example embodiment~~ the bispecific antibody has a first binding part comprising a heavy chain and a second binding part comprising a heavy chain wherein the heavy chain in each binding part is the same (i.e. a common heavy chain). In one ~~embodiment example~~ the common heavy chain variable region comprises as CDRs CDRH1 of SEQ ID NO: 2, CDRH2 of SEQ ID NO: 3, and CDRH3 of SEQ ID NO: 4. In one ~~example embodiment~~ the common heavy chain variable region is of SEQ ID NO: 1. In one ~~example embodiment~~ the common constant heavy chain is of SEQ ID NO: 30. In one ~~example embodiment~~ the common heavy chain is of SEQ ID NO: 43. In one ~~example embodiment~~ the common heavy chain is of SEQ ID NO: 44. In one ~~example embodiment~~ the common heavy chain is of SEQ ID NO: 45.

In one ~~example embodiment~~ the bispecific antibody is characterized in comprising in the first binding part and the second binding part as heavy chain a common heavy chain, comprising in the first binding part as light chain a kappa light chain, and in the second binding part as light chain a lambda light chain. In one ~~example embodiment~~ the light chain of the second binding part is of SEQ ID NO: 28 and the heavy chain of the second binding part is of SEQ ID NO: 45 (e.g. AB1 and AB-1L3-1/N derived bispecific antibodies like AB13L3-1/N, AB14L3-1/N, AB15L3-1/N, AB17L3-1/N, AB20L3-1/N, AB54L3-1/N, AB60L3-1/N, AB66L3-1/N, AB71L3-1/N, AB72L3-1/N, and AB73L3-1/N; for CDR and VL sequences see sequence list).

AB13,14,15 etc. denote for a first binding part (anti-CEACAM5 antibody arms) and L3-1 denotes for a second binding part (anti-CD3 antibody arm, also called 1A4) of bispecific antibodies of this invention. Any ABXX anti CEA arm can be combined with the L3-1 anti CD3 arm to form a bispecific antibody: e.g. ABXXL3-1 denotes a CEAXCD3 bispecific antibody according to the invention, comprising a WT hIgG1 Fc part; ABXXL3-1/D denotes a CEAXCD3 bispecific antibody according to the invention, comprising a hIgG1 Fc part carrying the L234A + L235A mutations; ABXXL3-1/N denotes a CEAXCD3 bispecific antibody according to the invention, comprising a hIgG1 Fc part carrying the L234A + L235A + P329A mutations.

In one ~~example embodiment~~ the bispecific antibody is characterized in comprising in the first binding part and the second binding part as heavy chain a common heavy chain, comprising in the first binding part as light chain variable region a lambda type region and as light chain constant region

a kappa type region (“hybrid format light chain”), and in the second binding part as light chain a lambda light chain (e.g. L3-1AB8 H-CK5 /D see figure 2 and description of figure 2).

In one ~~example embodiment~~ the bispecific antibody is characterized in comprising in the first binding part and the second binding part as heavy chain a common heavy chain, comprising in the first binding part as light chain variable region a lambda type region and as light chain constant region a lambda type region, and in the second binding part as light chain variable region a lambda type region and as light chain constant region a kappa type region (“hybrid format light chain”); e.g. AB8L3-1 H-CK5/D.

The bispecific antibodies ~~of the invention~~ disclosed herein show low binding/cross-reactivity to CEACAM family members other than CEACAM5. In one ~~example embodiment~~ the bispecific antibody is characterized in that the MFI value for binding to PEAKrapid cells (ATCC® CRL-2828™) expressing a CEACAM selected from the group consisting of CEACAM1, CEACAM3, CEACAM4, CEACAM6, CEACAM7, CEACAM8, CEACAM16, CEACAM18, CEACAM19, CEACAM20, and CEACAM21 is no more than 2 times compared to the MFI value for binding to WT PEAK cells (that is, untransfected PEAK cells) under the same experimental conditions. In one ~~example embodiment~~ the bispecific antibody is characterized in that the MFI value for binding to PEAKrapid cells expressing a CEACAM selected from the group consisting of CEACAM1, CEACAM3, CEACAM4, CEACAM6, and CEACAM8 is no more than 2 times compared to the MFI value for binding to WT PEAK cells under the same experimental conditions. In one ~~example embodiment~~ the bispecific antibody is characterized in that the MFI value for binding to PEAKrapid cells expressing CEACAM8 is no more than 2 times compared to the MFI value for binding to WT PEAK cells under the same experimental conditions. The experimental procedure for transfection of the PEAK cells and measuring of the binding of antibodies to these PEAK cells is described in Examples 1 and 5.

In one ~~example embodiment~~ the bispecific antibody binds to MKN-45 cells (DSMZ No: ACC 409) with an EC50 value of 0.5 nM to 50 nM. In one ~~example embodiment~~ the bispecific antibody binds to MKN-45 cells with an EC50 value of 0.5 nM to 30 nM. In one ~~example embodiment~~ the bispecific antibody ~~according to the invention~~ is characterized in that the MFI value for binding to MKN-45 cells at 200 nM, 1000 nM and 5000 nM is at least double of the MFI value obtained with TCB2014. The

binding assay is described in Example 7a. In one ~~example embodiment~~ the EC50 for the killing of tumor cell line MKN-45 measured in the assay containing human PBMC is for the bispecific antibodies of this invention 40% or more lower than the EC50 measured for TCB2014. In one ~~example embodiment~~ the EC50 for the killing of tumor cell line LS-174T measured in the assay containing human PBMC is for the bispecific antibodies ~~of this invention~~ disclosed herein 40% or more lower than the EC50 measured for TCB2014.

In one ~~example embodiment~~ the bispecific antibody is killing LS174T cells in an assay containing human PBMC in a concentration dependent manner with an EC50 value of 0.01 to 10 nM. In one ~~example embodiment~~ the bispecific antibody is killing LS174T cells in an assay containing human PBMC in a concentration dependent manner with an EC50 value of 0.01 to 1 nM.

An assay for measuring T-cell retargeted lysis/killing of CEA-positive cells is described in Example 8.

In one ~~example embodiment~~ the bispecific antibody is characterized in that the EC50 value in the same assay (killing of CEA positive LS174T tumor cells) is not increased by more than a factor of 20, in one ~~example embodiment~~ not more than 15, and in one ~~example embodiment~~ not more than 10, in presence of 5 µg/ml soluble CEACAM5, compared to the EC50 value for lysis without soluble CEACAM5 under the same experimental conditions.

In another ~~example embodiment~~ the bispecific antibody is characterized in that the EC50 value in the same assay is not increased by more than a factor of 10, in one ~~example embodiment~~ not more than 5, in presence of 1 µg/ml soluble CEACAM5, compared to the EC50 value for lysis without soluble CEACAM5 under the same experimental conditions.

In one ~~example embodiment~~ the bispecific antibody is characterized in that said bispecific antibody inhibits tumor volume growth in a HPAF-II model until day 18 by 25% or more, compared to tumor volume growth in the vehicle group under the same experimental conditions.

In one ~~example embodiment~~ the bispecific antibody is characterized in that said bispecific antibody inhibits tumor volume growth in a HPAF-II model until day 18 similar, and not different in a statistically

significant manner, compared to TCB2014 under the same experimental conditions. The mouse tumor model is described in Example 9a.

In one ~~example embodiment~~ the bispecific antibody comprises in each subunit of the Fc domain amino acid substitutions that reduce binding to an activating Fc receptor and/or reduce effector function wherein said amino acid substitutions are L234A and L235A and/or a substitution of P329, selected from the group consisting of P329A, P329G and P329R (Kabat EU index numbering). In one ~~example embodiment~~ the bispecific antibody comprises in each subunit of the Fc domain amino acid substitutions L234A and L235A and P329A (Kabat EU index numbering). L234A and L235A (LALA) means that amino acid leucine at position 234/235 is replaced by alanine. P329A (PA) means that amino acid proline at position 329 is replaced by alanine.

In one ~~example embodiment~~ the bispecific antibody comprises a common heavy chain. In one ~~example embodiment~~ the bispecific antibody comprises a common heavy chain comprising as CDRs CDRH1 of SEQ ID NO: 2, as CDRH2 of SEQ ID NO: 3 and as CDRH3 of SEQ ID NO: 4. In one ~~example embodiment~~ the bispecific antibody comprises in the second binding part a light chain region comprising as CDRs CDRL1 of SEQ ID NO: 18, CDRL2 of SEQ ID NO: 19, and CDRL3 of SEQ ID NO: 20.

In one ~~example embodiment~~ the bispecific antibody comprises in the first binding part as light chain constant region a region of SEQ ID NO: 39. In one ~~example embodiment~~ the bispecific antibody comprises in the first binding part as light chain constant region a region of SEQ ID NO: 41. In one ~~example embodiment~~ the bispecific antibody comprises in the first binding part as light chain constant region a region of SEQ ID NO: 58. In one ~~example embodiment~~ the bispecific antibody comprises a common heavy chain of SEQ ID NO: 43 or a common heavy chain of SEQ ID NO: 44 or a common heavy chain of SEQ ID NO: 45. In one ~~example embodiment~~ the bispecific antibody comprises in the first binding part as light chain constant region a region of SEQ ID NO: 39 and a common heavy chain of SEQ ID of SEQ ID NO: 45.

In one ~~example embodiment~~ the bispecific antibody comprises in the second binding part as light chain a light chain selected from the group consisting of SEQ ID NOs: 25, 26, 27, 28, and 29 or from the hybrid format light chain (LC) group of SEQ ID NOs: 67, 68, 69, 70, and 71.

In one ~~example embodiment~~ the bispecific antibody comprises in the first binding part as light chain constant region a region of SEQ ID NO: 39, a common heavy chain of SEQ ID NO: 45, and in the second binding part a light chain of SEQ ID NO: 28.

- 5 In one ~~example embodiment~~ the bispecific antibody competes with an anti-CEA antibody, selected from the group consisting of an anti-CEA antibody, comprising as VL and VH domains VL and VH of sequences SEQ ID NOs: 48 and 49 (anti-CEA antibody MEDI), comprising as VL and VH domains VL and VH of sequences SEQ ID NOs: 46 and 47 (antibody SM3E), comprising as VL and VH domains VL and VH of sequences SEQ ID NOs: 56 and 57 (Labetuzumab (Lab)),
10 comprising as VL and VH domains VL and VH of sequences SEQ ID NOs: 50 and 51 (SAR), comprising as VL and VH domains VL and VH of sequences SEQ ID NOs: 54 and 55 (T86.66), and comprising as VL and VH domains VL and VH of sequences SEQ ID NOs: 52 and 53 (CH1A1A). See also figure 1 and Example 5c).
- 15 Examples for antibodies useful as CEA VL or CL regions in bispecific antibodies according to the invention and competing with MEDI for the binding to recombinant CEA are anti-CEA antibody AB1 and antibodies obtained by lead optimizing of AB1 (see Example 11 for the experimental method). Anti-CEA antibodies AB13, 14, 15, 17, 20, 54, 60, 66, 71, 72, 73 and the respective bispecific anti CEAxCD3 antibodies AB13L3-1, AB14L3-1, AB15L3-1, AB17L3-1, AB20L3-1,
20 AB54L3-1, AB60L3-1, AB66L3-1, AB71L3-1, AB72L3-1, and AB73L3-1 are competing in the same manner as antibody AB1 resp. AB1L3-1. Examples for antibodies useful as CEA VL or CL regions in bispecific antibodies according to the invention and competing with SM3E for the binding to recombinant CEA are anti-CEA antibody AB8 and antibodies obtained by oligonucleotide-directed mutagenesis of AB8, using degenerated oligonucleotides. Examples for
25 antibodies useful as CEA VL or CL regions in bispecific antibodies according to the invention and competing with T84.66 for the binding to recombinant CEA are anti-CEA antibody 1B4 and antibodies obtained by oligonucleotide-directed mutagenesis of 1B4, using degenerated oligonucleotides.
- 30 Examples for antibodies useful as CEA VL or CL regions in bispecific antibodies according to the invention but not competing with any of the reference antibodies for the binding to

recombinant CEA are anti-CEA antibody C11 and antibodies obtained by oligonucleotide-directed mutagenesis of C11, using degenerated oligonucleotides.

AB1 is an anti-CEA antibody with the HC SEQ ID NO: 43 and the kappa LC SEQ ID NO: 40,
5 encoded by the nucleic acid sequences shown in SEQ ID NOs: 80 and 78, respectively.

AB8 is an anti-CEA antibody with the HC SEQ ID NO: 43 and the lambda LC SEQ ID NO: 42,
encoded by the nucleic acid sequences shown in SEQ ID NOs: 80 and 79, respectively.

10 1B4 is an anti-CEA antibody with the HC SEQ ID NO: 43 and the lambda LC SEQ ID NO: 74,
encoded by the nucleic acid sequences shown in SEQ ID NO: 80 and 77, respectively.

C11 is an anti-CEA antibody with the HC SEQ ID NO: 43 and the kappa LC SEQ ID NO: 73,
encoded by the nucleic acid sequences shown in SEQ ID NO: 80 and 76, respectively.

15 A CEA light chain useful as kappa light chain is of SEQ ID NO: 40. A CEA light chain useful as
kappa light chain is of SEQ ID NO: 73. A CEA light chain useful as lambda light chain is of SEQ
ID NO: 74. A CEA light chain useful as hybrid kappa light chain is of SEQ ID NO: 75.

20 In one example embodiment the bispecific antibody comprises in each subunit of the Fc domain
up to three amino acid substitutions that reduce binding to an activating Fc receptor and/or effector
function wherein said amino acid substitutions are L234A, L235A and a substitution of P329,
selected from the group consisting of P329A, P329G and P329R (Kabat EU index numbering). In
one example embodiment the common heavy chain of the antibody ~~according to the~~
25 ~~invention disclosed herein~~ is of SEQ ID NOs: 43, 44, or 45. In one example embodiment the
common heavy chain of the antibody according to the ~~invention disclosure~~ is of SEQ ID NO: 45
(L234A, L235A, and P329A).

30 In one example embodiment the bispecific antibody shows one or more properties selected from
the group of a) binding to MKN-45 cells with an EC50 value of 0.5 nM to 50 nM, b1) competing
with an anti-CEA antibody, comprising as VL and VH domains VL and VH of sequences SEQ ID
NOs: 48 and 49 (MEDI), or b2) competing with an anti-CEA antibody, comprising as VL and VH
domains VL and VH of sequences SEQ ID NOs: 46 and 47 (SM3E), or b3) competing with an

anti-CEA antibody, comprising as VL and VH domains VL and CH of sequences SEQ ID NOs: 54 and 55 (T84.66), or b4) not competing with any of the tool antibodies (see Example 5c for the tool antibodies) c) comprising in each subunit of the Fc domain amino acid substitutions that reduce binding to an activating Fc receptor and/or effector function wherein said amino acid substitutions are L234A and L235A and a substitution of P329, selected from the group consisting of P329A, P329G and P329R (Kabat EU index numbering), d) killing MKN-45, HPAF-II, and/or LS174T cells in an assay containing human PBMC in a concentration dependent manner with an EC50 value of 0.01 to 10 nM.

10 In one ~~example embodiment~~ the bispecific antibody shows one or more properties selected from the group of

a) binding to MKN-45 cells with an EC50 value of 0.5 nM to 50 nM,

b) killing MKN-45, HPAF-II, or LS174T cells in an assay containing human PBMC in a concentration dependent manner with an EC50 value of 0.01 to 10 nM,

15 c) binding to CEACAM5 expressing PEAK cells, but not cross reacting with CEACAM8 expressing PEAK cells,

d) the killing EC50 in the TDCC assay (Example 8) when LS174T tumor cells are used as target cells is not increased by more than a factor 5 in presence of 1 µg/mL of sCEA,

e) inhibiting tumor growth in a HPAF-II model by 25% or more compared to the control group (vehicle only),

20 f) competing with an anti-CEA antibody, comprising as VL and VH domains VL and VH of sequences SEQ ID NOs: 48 and 49 (MEDI), and

g) comprising in each subunit of the Fc domain amino acid substitutions L234A, L235A and P329A (Kabat EU index numbering).

25 In one ~~example embodiment~~ the bispecific antibody shows the properties of a) to d). In one ~~example embodiment~~ the bispecific antibody shows all properties of a) to f). In one ~~example embodiment~~ the bispecific antibody shows the properties of a) to d) and g). In one ~~example embodiment~~ the bispecific antibody shows the properties of a) to d) and f) and g). In one ~~example embodiment~~ the bispecific antibody shows all properties of a) to g).

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In one ~~example embodiment~~ the bispecific antibody is characterized in comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3ε, characterized in that

a) the first binding part and the second binding part comprise each as heavy chain a common heavy chain (cHC) and comprises as variable region a variable region which comprises as CDRH1, CDRH2, and CDRH3, a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b) the first binding part comprises

i) a kappa light chain constant region (CL), and a light chain variable region (VL), comprising as CDRL1, CDRL2 and CDRL3, a CDRL1 of SEQ ID NO: 32, a CDRL2 of SEQ ID NO: 33 and a CDRL3 of SEQ ID NO: 34 or a light chain variable region derived from SEQ ID NO: 31 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides,

c) the second binding part comprises a light chain variable region, comprising as CDRL1, CDRL2 and CDRL3 a group of CDRs selected from the group consisting of

I) CDRL1 of SEQ ID NO: 6, a CDRL2 of SEQ ID NO: 7 and a CDRL3 of SEQ ID NO: 8,

II) CDRL1 of SEQ ID NO: 10, a CDRL2 of SEQ ID NO: 11 and a CDRL3 of SEQ ID NO: 12,

III) CDRL1 of SEQ ID NO: 14, a CDRL2 of SEQ ID NO: 15 and a CDRL3 of SEQ ID NO: 16,

IV) CDRL1 of SEQ ID NO: 18, a CDRL2 of SEQ ID NO: 19 and a CDRL3 of SEQ ID NO: 20, and

V) CDRL1 of SEQ ID NO: 22, a CDRL2 of SEQ ID NO: 23 and a CDRL3 of SEQ ID NO: 24.

d) the second binding part comprises a lambda light chain constant region.

In one ~~example embodiment~~ the second binding part in c) comprises a light chain selected from the group consisting of SEQ ID NOs: 25, 26, 27, 28, and 29.

In one ~~example embodiment~~ the bispecific antibody is characterized in comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3ε, characterized in that

a) the first binding part and the second binding part comprise each as heavy chain a heavy chain which comprises as CDRH1, CDRH2, and CDRH3, a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b) the first binding part comprises a light chain variable region (VL), comprising as CDRs a CDRL1 derived from SEQ ID NO: 32 by oligonucleotide-directed mutagenesis using

degenerated oligonucleotides and comprising up to four amino acid substitutions, a CDRL2 derived from SEQ ID NO: 33 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides and comprising up to four amino acid substitutions, a CDRL3 derived from SEQ ID NO: 34 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides and comprising up to four amino acid substitutions,

c) the second binding part comprises a light chain variable region, comprising as CDRL1, CDRL2 and CDRL3 a CDRL1 of SEQ ID NO: 18, a CDRL2 of SEQ ID NO: 19 and a CDRL3 of SEQ ID NO: 20.

Such bispecific antibodies are, but not limited, bispecific anti CEAxCD3 antibodies AB13L3-1, AB14L3-1, AB15L3-1, AB17L3-1, AB20L3-1, AB54L3-1, AB60L3-1, AB66L3-1, AB71L3-1, AB72L3-1, and AB73L3-1.

In one aspect, the present disclosure refers to an embodiment the bispecific antibody is characterized in comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3ε, characterized in that:

a) the first binding part comprises a heavy chain variable region VH, which comprises as CDRH1, CDRH2, and CDRH3 a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b) the first binding part comprises as light chain variable region a light chain variable region comprising a CDRL set selected from the group consisting of

b1) a CDRL1 of SEQ ID NO: 32, CDRL2 of SEQ ID NO: 33, and CDRL3 of SEQ ID NO: 34,

b2) a CDRL1 of SEQ ID NO: 81, CDRL2 of SEQ ID NO: 82, and CDRL3 of SEQ ID NO: 83,

b3) a CDRL1 of SEQ ID NO: 84, CDRL2 of SEQ ID NO: 85, and CDRL3 of SEQ ID NO: 86,

b4) a CDRL1 of SEQ ID NO: 87, CDRL2 of SEQ ID NO: 88, and CDRL3 of SEQ ID NO: 89,

b5) a CDRL1 of SEQ ID NO: 90, CDRL2 of SEQ ID NO: 91, and CDRL3 of SEQ ID NO: 92,

b6) a CDRL1 of SEQ ID NO: 93, CDRL2 of SEQ ID NO: 94, and CDRL3 of SEQ ID NO: 95,

b7) a CDRL1 of SEQ ID NO: 96, CDRL2 of SEQ ID NO: 97, and CDRL3 of SEQ ID NO: 98,

b8) a CDRL1 of SEQ ID NO: 99, CDRL2 of SEQ ID NO: 100, and CDRL3 of SEQ ID NO: 101,

b9) a CDRL1 of SEQ ID NO: 102, CDRL2 of SEQ ID NO: 103, and CDRL3 of SEQ ID NO: 104,

b10) a CDRL1 of SEQ ID NO: 105, CDRL2 of SEQ ID NO: 106, and CDRL3 of SEQ ID NO: 107,

b11) a CDRL1 of SEQ ID NO: 108, CDRL2 of SEQ ID NO: 109, and CDRL3 of SEQ ID NO: 110, and

5 b12) a CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, and CDRL3 of SEQ ID NO: 113, and

c) the second binding part comprises a heavy chain variable region VH comprising a CDRH1 of SEQ ID NO: 2, CDRH2 of SEQ ID NO: 3 and CDRH3 of SEQ ID NO: 4 and a light chain variable region VL comprising a CDRL1 of SEQ ID NO: 18, CDRL2 of SEQ ID NO: 19, and CDRL3 of
10 SEQ ID NO: 20.

In one ~~example embodiment~~ the bispecific antibody is characterized in comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3ε, characterized in that:

15 a) the first binding part comprises a heavy chain variable region VH, which comprises as CDRH1, CDRH2, and CDRH3 a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b) the first binding part comprises as light chain variable region a light chain variable region comprising a CDRL set selected from the group consisting of

20 b1) a CDRL1 of SEQ ID NO: 90, CDRL2 of SEQ ID NO: 91, and CDRL3 of SEQ ID NO: 92,

b2) a CDRL1 of SEQ ID NO: 96, CDRL2 of SEQ ID NO: 97, and CDRL3 of SEQ ID NO: 98,

b3) a CDRL1 of SEQ ID NO: 99, CDRL2 of SEQ ID NO: 100, and CDRL3 of SEQ ID NO: 101,

b4) a CDRL1 of SEQ ID NO: 102, CDRL2 of SEQ ID NO: 103, and CDRL3 of SEQ ID NO: 104,

b5) a CDRL1 of SEQ ID NO: 105, CDRL2 of SEQ ID NO: 106, and CDRL3 of SEQ ID NO: 107,

25 and

b6) a CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, and CDRL3 of SEQ ID NO: 113, and

c) the second binding part comprises a heavy chain variable region VH comprising a CDRH1 of SEQ ID NO: 2, CDRH2 of SEQ ID NO: 3 and CDRH3 of SEQ ID NO: 4 and a light chain variable region VL comprising a CDRL1 of SEQ ID NO: 18, CDRL2 of SEQ ID NO: 19, and CDRL3 of
30 SEQ ID NO: 20.

In one ~~example embodiment~~ the bispecific antibody is characterized in comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3ε, characterized in that:

a) the first binding part comprises a heavy chain variable region VH, which comprises as CDRH1, CDRH2, and CDRH3 a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b) the first binding part comprises as light chain variable region a light chain variable region comprising a CDRL set selected from the group consisting of

b1) a CDRL1 of SEQ ID NO: 90, CDRL2 of SEQ ID NO: 91, and CDRL3 of SEQ ID NO: 92,

b2) a CDRL1 of SEQ ID NO: 105, CDRL2 of SEQ ID NO: 106, and CDRL3 of SEQ ID NO: 107, and

b3) a CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, and CDRL3 of SEQ ID NO: 113, and

c) the second binding part comprises a heavy chain variable region VH comprising a CDRH1 of SEQ ID NO: 2, CDRH2 of SEQ ID NO: 3 and CDRH3 of SEQ ID NO: 4 and a light chain variable region VL comprising a CDRL1 of SEQ ID NO: 18, CDRL2 of SEQ ID NO: 19, and CDRL3 of SEQ ID NO: 20.

In one ~~example embodiment~~, the ~~disclosure invention~~ relates to a bispecific antibody according to the ~~disclosure invention~~, characterized in comprising

a) in the first binding part a heavy chain variable region VH having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 1, comprising a CDR1 of SEQ ID NO: 2, a CDR2 of SEQ ID NO: 3, and a CDR3 of SEQ ID NO: 4, and

b) a light chain variable region VL selected from the group consisting of

b1) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 31 and comprising a CDRL1 of SEQ ID NO: 32, CDRL2 of SEQ ID NO: 33, and CDRL3 of SEQ ID NO: 34,

b2) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 114 and comprising a CDRL1 of SEQ ID NO: 81, CDRL2 of SEQ ID NO: 82, and CDRL3 of SEQ ID NO: 83,

NO: 3, and a CDR3 of SEQ ID NO: 4, and a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 17, comprising a CDRL1 of SEQ ID NO: 18, CDRL2 of SEQ ID NO: 19, and CDRL3 of SEQ ID NO: 20.

- 5 In one ~~example~~embodiment, the ~~invention relates to~~disclosure describes a bispecific antibody according to the ~~invention~~as disclosed herein, characterized in comprising
- a) in the first binding part a heavy chain variable region VH SEQ ID NO: 1, and
 - b) a light chain variable region VL selected from the group consisting of
 - b1) a light chain variable region VL of SEQ ID NO: 31,
 - 10 b2) a light chain variable region VL of SEQ ID NO: 114,
 - b3) a light chain variable region VL of SEQ ID NO: 115,
 - b4) a light chain variable region VL of SEQ ID NO: 116,
 - b5) a light chain variable region VL of SEQ ID NO: 117,
 - b6) a light chain variable region VL of SEQ ID NO: 118,
 - 15 b7) a light chain variable region VL of SEQ ID NO: 119,
 - b8) a light chain variable region VL of SEQ ID NO: 120,
 - b9) a light chain variable region VL of SEQ ID NO: 121,
 - b10) a light chain variable region VL of SEQ ID NO: 122,
 - b11) a light chain variable region VL of SEQ ID NO: 123, and
 - 20 b12) a light chain variable region VL of SEQ ID NO: 124, and
 - c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light chain variable region VL of SEQ ID NO: 17.

- 25 In one ~~example~~embodiment, the ~~disclosure invention~~relates to a bispecific antibody according to the ~~disclosure invention~~, characterized in comprising
- a) in the first binding part a heavy chain variable region VH SEQ ID NO: 1, and
 - b) a light chain variable region VL selected from the group consisting of
 - b1) a light chain variable region VL of SEQ ID NO: 117,
 - b2) a light chain variable region VL of SEQ ID NO: 119,
 - 30 b3) a light chain variable region VL of SEQ ID NO: 120,
 - b4) a light chain variable region VL of SEQ ID NO: 121,
 - b5) a light chain variable region VL of SEQ ID NO: 122, and

b6) a light chain variable region VL of SEQ ID NO: 124, and

c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light chain variable region VL of SEQ ID NO: 17.

5 In one ~~example~~embodiment, the ~~invention relates~~disclosure refers to a bispecific antibody ~~according to the invention~~, characterized in comprising

a) in the first binding part a heavy chain variable region VH SEQ ID NO: 1, and

b) a light chain variable region VL selected from the group consisting of

b1) a light chain variable region VL of SEQ ID NO: 117,

10 b2) a light chain variable region VL of SEQ ID NO: 122, and

b3) a light chain variable region VL of SEQ ID NO: 124, and

c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light chain variable region VL of SEQ ID NO: 17.

15 In one ~~embodiment~~aspect, the ~~invention relates~~disclosure refers to a bispecific antibody ~~according to the invention~~, characterized in comprising in the first binding part

a) a heavy chain variable region VH SEQ ID NO: 1, and

b) a light chain selected from the group consisting of

b1) the light chain of SEQ ID NO: 40

20 b2) the light chain of SEQ ID NO: 125,

b3) the light chain of SEQ ID NO: 126,

b4) the light chain of SEQ ID NO: 127,

b5) the light chain of SEQ ID NO: 128,

b6) the light chain of SEQ ID NO: 129,

25 b7) the light chain of SEQ ID NO: 130,

b8) the light chain of SEQ ID NO: 131

b9) the light chain of SEQ ID NO: 132,

b10) the light chain of SEQ ID NO: 133, and

b11) the light chain of SEQ ID NO: 134, and

30 b12) the light chain of SEQ ID NO: 135, and

c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light chain of SEQ ID NO: 28.

In one ~~example embodiment~~, the ~~invention relates disclosure~~ refers to a bispecific antibody according to the ~~invention~~, characterized in comprising in the first binding part

a) a common heavy chain selected from the group consisting of

a1) the heavy chain of SEQ ID NO: 43,

5 a2) the heavy chain of SEQ ID NO: 44, or

a3) the heavy chain of SEQ ID NO: 45, and

b) a light chain selected from the group consisting of

b1) the light chain of SEQ ID NO: 40

b2) the light chain of SEQ ID NO: 125,

10 b3) the light chain of SEQ ID NO: 126,

b4) the light chain of SEQ ID NO: 127,

b5) the light chain of SEQ ID NO: 128,

b6) the light chain of SEQ ID NO: 129,

b7) the light chain of SEQ ID NO: 130,

15 b8) the light chain of SEQ ID NO: 131

b9) the light chain of SEQ ID NO: 132,

b10) the light chain of SEQ ID NO: 133

b11) the light chain of SEQ ID NO: 134, or

b12) the light chain of SEQ ID NO: 135, and

20 c) in the second binding part a light chain of SEQ ID NO: 28.

In one ~~example embodiment~~ a bispecific antibody according to the ~~invention disclosure~~ (AB17L3-1/N) comprises a common heavy chain of SEQ ID NO: 45 (/N) and in the second binding part as

light chain a light chain of SEQ ID NO: 28 (1A4 LC respectively L3-1) and in the first binding

25 part as light chain a light chain of SEQ ID NO: 128 (AB17). In one ~~example embodiment~~ a

bispecific antibody according to the ~~invention disclosure~~ (AB71L3-1/N) comprises a common

heavy chain of SEQ ID NO: 45 (/N) and in the second binding part as light chain a light chain of

SEQ ID NO: 28 (L3-1) and in the first binding part as light chain a light chain of SEQ ID NO: 133

(AB71). In one ~~example embodiment~~ a bispecific antibody according to the ~~invention disclosure~~

30 (AB73L3-1/N) comprises a common heavy chain of SEQ ID NO: 45 (/N) and in the second binding

part as light chain a light chain of SEQ ID NO: 28 (L3-1) and in the first binding part as light chain

a light chain of SEQ ID NO: 135 (AB73).

In one ~~example embodiment~~ the bispecific antibody is characterized in comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3ε, characterized in that

a) the first binding part and the second binding part comprise each as heavy chain a common heavy chain and comprises as variable region a variable region which comprises as CDRH1, CDRH2, and CDRH3, a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b) the first binding part comprises

i) a lambda light chain constant region (CL) and

ii) a light chain variable region (VL), comprising as CDRL1, CDRL2 and CDRL3, a CDRL1 of SEQ ID NO: 36, a CDRL2 of SEQ ID NO: 37 and a CDRL3 of SEQ ID NO: 38 or a light chain variable region derived from SEQ ID NO: 35 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides,

c) the second binding part comprises a light chain variable region, comprising as CDRL1, CDRL2 and CDRL3 a group of CDRs selected from the group consisting of

I) CDRL1 of SEQ ID NO: 6, a CDRL2 of SEQ ID NO: 7 and a CDRL3 of SEQ ID NO: 8,

II) CDRL1 of SEQ ID NO: 10, a CDRL2 of SEQ ID NO: 11 and a CDRL3 of SEQ ID NO: 12,

III) CDRL1 of SEQ ID NO: 14, a CDRL2 of SEQ ID NO: 15 and a CDRL3 of SEQ ID NO: 16,

IV) CDRL1 of SEQ ID NO: 18, a CDRL2 of SEQ ID NO: 19 and a CDRL3 of SEQ ID NO: 20, and

V) CDRL1 of SEQ ID NO: 22, a CDRL2 of SEQ ID NO: 23 and a CDRL3 of SEQ ID NO: 24.

d) the second binding part comprises a hybrid-kappa chain constant region.

In one ~~example embodiment~~ the second binding part in c) comprises a light chain selected from the group consisting of SEQ ID NOs: 67, 68, 69, 70, and 71

In one ~~example embodiment~~ the second binding part can comprise as light chain constant region a lambda light chain constant region of SEQ ID NO: 41; in that case the first binding part comprises in one ~~example embodiment~~ as light chain constant region a hybrid-kappa light chain region of SEQ ID NO: 58. In one ~~example embodiment~~ the arm carrying the hybrid light chain constant region is based on the overall properties of the bsAb, including but not limited to stability and productivity.

In one ~~example embodiment~~ the light chain variable region of the first binding part is derived from SEQ ID NO: 35 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides, the common heavy chain is of SEQ ID NO: 45, and the variable region of the common heavy chain is of SEQ ID NO: 1.

5

In one ~~example embodiment~~ the bispecific antibody is characterized in comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3ε, characterized in that

a) the first binding part and the second binding part comprise each as heavy chain a common heavy chain and comprises as variable region a variable region which comprises as CDRH1, CDRH2, and CDRH3, a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b) the first binding part comprises

i) a kappa light chain constant region (CL), and
ii) a light chain variable region (VL), comprising as CDRL1, CDRL2 and CDRL3, a CDRL1 of SEQ ID NO: 64, a CDRL2 of SEQ ID NO: 65 and a CDRL3 of SEQ ID NO: 66 or a light chain variable region derived from SEQ ID NO: 63 by oligonucleotide-directed mutagenesis,

c) the second binding part comprises a light chain variable region, comprising as CDRL1, CDRL2 and CDRL3 a group of CDRs selected from the group consisting of

I) CDRL1 of SEQ ID NO: 6, a CDRL2 of SEQ ID NO: 7 and a CDRL3 of SEQ ID NO: 8,
II) CDRL1 of SEQ ID NO: 10, a CDRL2 of SEQ ID NO: 11 and a CDRL3 of SEQ ID NO: 12,
III) CDRL1 of SEQ ID NO: 14, a CDRL2 of SEQ ID NO: 15 and a CDRL3 of SEQ ID NO: 16,
IV) CDRL1 of SEQ ID NO: 18, a CDRL2 of SEQ ID NO: 19 and a CDRL3 of SEQ ID NO: 20,
and

V) CDRL1 of SEQ ID NO: 22, a CDRL2 of SEQ ID NO: 23 and a CDRL3 of SEQ ID NO: 24.

d) the second binding part comprises a lambda light chain constant region.

In one ~~example embodiment~~ the second binding part in c) comprises a light chain selected from the group consisting of SEQ ID NOs: 25, 26, 27, 28, and 29.

30

In one ~~example embodiment~~ of the ~~invention~~disclosure the light chain variable region of the first binding part is derived from SEQ ID NO: 63 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides, the common heavy chain is of SEQ ID NO: 45.

5 In one ~~example embodiment~~ the bispecific antibody is characterized in comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3ε, characterized in that

a) the first binding part and the second binding part comprise each as heavy chain a common heavy chain and comprises as variable region a variable region which comprises as CDRH1, CDRH2,
10 and CDRH3, a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b) the first binding part a lambda light chain constant region (CL), and a light chain variable region (VL), comprising as CDRL1, CDRL2 and CDRL3, a CDRL1 of SEQ ID NO: 60, a CDRL2 of
15 SEQ ID NO: 61 and a CDRL3 of SEQ ID NO: 62 or a light chain variable region derived from SEQ ID NO: 59 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides,

c) the second binding part comprises a light chain variable region, comprising as CDRL1, CDRL2 and CDRL3 a group of CDRs selected from the group consisting of

I) CDRL1 of SEQ ID NO: 6, a CDRL2 of SEQ ID NO: 7 and a CDRL3 of SEQ ID NO: 8,

II) CDRL1 of SEQ ID NO: 10, a CDRL2 of SEQ ID NO: 11 and a CDRL3 of SEQ ID NO: 12,

20 III) CDRL1 of SEQ ID NO: 14, a CDRL2 of SEQ ID NO: 15 and a CDRL3 of SEQ ID NO: 16,

IV) CDRL1 of SEQ ID NO: 18, a CDRL2 of SEQ ID NO: 19 and a CDRL3 of SEQ ID NO: 20,
and

V) CDRL1 of SEQ ID NO: 22, a CDRL2 of SEQ ID NO: 23 and a CDRL3 of SEQ ID NO: 24.

d) the second binding part comprises a hybrid-kappa chain constant region.

25 In a further ~~example embodiment~~ of the ~~invention~~disclosure, the second binding part comprise as light chain constant region a lambda light constant chain region of SEQ ID NO: 41; in that case the first binding part comprises in one ~~example embodiment~~ as light chain constant region a hybrid-kappa light chain constant region of SEQ ID NO: 58. The choice of the arm carrying the hybrid
30 light chain constant region is based on the overall properties of the final bsAb, including but not limited to stability and productivity.

In one ~~example embodiment~~ the light chain variable region of the first binding part is derived from SEQ ID NO: 59 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides.

In one ~~example embodiment~~ the bispecific antibody is characterized in comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3ε, characterized in that

a) the first binding part and the second binding part comprise each as heavy chain a common heavy chain) and comprises as variable region a variable region which comprises as CDRH1, CDRH2, and CDRH3, a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b) the first binding part comprises a light chain constant region of human kappa type and a light chain variable region of human kappa type, comprising as CDRL1, CDRL2 and CDRL3 a CDRL1 of SEQ ID NO: 32 with substitution of 0, 1, 2, 3, or 4 amino acids, a CDRL2 of SEQ ID NO: 33 with substitution of 0, 1, 2, 3 or 4 amino acids, and a CDRL3 of SEQ ID NO: 34 with substitution of 0, 1, 2, 3, 4, or 5 amino acids,

c) the second binding part comprises a light chain constant region of human lambda type and a light chain variable region of human lambda type, comprising as CDRL1, CDRL2 and CDRL3 a group of CDRs selected from the group consisting of

I) CDRL1 of SEQ ID NO: 6, a CDRL2 of SEQ ID NO: 7 and a CDRL3 of SEQ ID NO: 8,

II) CDRL1 of SEQ ID NO: 10, a CDRL2 of SEQ ID NO: 11 and a CDRL3 of SEQ ID NO: 12,

III) CDRL1 of SEQ ID NO: 14, a CDRL2 of SEQ ID NO: 15 and a CDRL3 of SEQ ID NO: 16,

IV) CDRL1 of SEQ ID NO: 18, a CDRL2 of SEQ ID NO: 19 and a CDRL3 of SEQ ID NO: 20, and

V) CDRL1 of SEQ ID NO: 22, a CDRL2 of SEQ ID NO: 23 and a CDRL3 of SEQ ID NO: 24.

In one ~~example embodiment~~ the second binding part in c) comprises a light chain selected from the group consisting of SEQ ID NOs: 25, 26, 27, 28, and 29.

In one ~~example embodiment~~ the bispecific antibody is characterized in comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3ε, characterized in that

a) the first binding part and the second binding part comprise each as heavy chain a common heavy chain and comprises as variable region a variable region which comprises as CDRH1, CDRH2, and CDRH3, a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

5 b) the first binding part comprises light chain constant region of human lambda type and a light chain variable region of human lambda type, comprising as CDRL1, CDRL2 and CDRL3, a CDRL set selected from the group consisting of a CDRL1 of SEQ ID NO: 36 with substitution of 0, 1, 2, 3, 4, or 5 amino acids, a CDRL2 of SEQ ID NO: 37 with substitution of 0, 1, 2, 3, 4, or 5 amino acids, and a CDRL3 of SEQ ID NO: 38, with substitution of 0, 1, 2, 3, 4, or 5 amino acids,

10 c) the second binding part comprises a hybrid kappa light chain constant region and a light chain variable region of human lambda type, comprising as CDRL1, CDRL2 and CDRL3 a group of CDRs selected from the group consisting of

I) CDRL1 of SEQ ID NO: 6, a CDRL2 of SEQ ID NO: 7 and a CDRL3 of SEQ ID NO: 8,

II) CDRL1 of SEQ ID NO: 10, a CDRL2 of SEQ ID NO: 11 and a CDRL3 of SEQ ID NO: 12,

15 III) CDRL1 of SEQ ID NO: 14, a CDRL2 of SEQ ID NO: 15 and a CDRL3 of SEQ ID NO: 16,

IV) CDRL1 of SEQ ID NO: 18, a CDRL2 of SEQ ID NO: 19 and a CDRL3 of SEQ ID NO: 20, and

V) CDRL1 of SEQ ID NO: 22, a CDRL2 of SEQ ID NO: 23 and a CDRL3 of SEQ ID NO: 24.

20 In one ~~example embodiment~~ the second binding part in c) comprises a light chain selected from the group consisting of SEQ ID NOs: 67, 68, 69, 70, and 71.

In one ~~example embodiment~~ the bispecific antibody is characterized in comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3ε, characterized in that

25 a) the first binding part and the second binding part comprise each as heavy chain a common heavy chain and comprises as variable region a variable region which comprises as CDRH1, CDRH2, and CDRH3, a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

30 b) the first binding part comprises a light chain constant region of human lambda type and a light chain variable region of human lambda type, comprising as CDRL1, CDRL2 and CDRL3, a CDRL set selected from the group consisting of a CDRL1 of SEQ ID NO: 60 with substitution of 0, 1, 2, 3, or 4 amino acids, a CDRL2 of SEQ ID NO: 61 with substitution of 0, 1, 2, 3 or 4

amino acids, and a CDRL3 of SEQ ID NO: 62 with substitution of 0, 1, 2, 3, 4, or 5 amino acids, and

c) the second binding part comprises a light chain constant region of human kappa type, and a light chain variable region of human lambda type, comprising as CDRL1, CDRL2 and CDRL3 a group of CDRs selected from the group consisting of

I) CDRL1 of SEQ ID NO: 6, a CDRL2 of SEQ ID NO: 7 and a CDRL3 of SEQ ID NO: 8,

II) CDRL1 of SEQ ID NO: 10, a CDRL2 of SEQ ID NO: 11 and a CDRL3 of SEQ ID NO: 12,

III) CDRL1 of SEQ ID NO: 14, a CDRL2 of SEQ ID NO: 15 and a CDRL3 of SEQ ID NO: 16,

IV) CDRL1 of SEQ ID NO: 18, a CDRL2 of SEQ ID NO: 19 and a CDRL3 of SEQ ID NO: 20,

and

V) CDRL1 of SEQ ID NO: 22, a CDRL2 of SEQ ID NO: 23 and a CDRL3 of SEQ ID NO: 24.

In one ~~example embodiment~~ the second binding part in c) comprises a light chain selected from the group consisting of SEQ ID NOs: 67, 68, 69, 70, and 71.

In one ~~example embodiment~~ the bispecific antibody is characterized in comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3ε, characterized in that

a) the first binding part and the second binding part comprise each as heavy chain a (common heavy chain and comprises as variable region a variable region which comprises as CDRH1, CDRH2, and CDRH3, a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b) the first binding part comprises a light chain constant region of human kappa type, and a light chain variable region of human kappa type, comprising as CDRL1, CDRL2 and CDRL3, a CDRL set selected from the group consisting of a CDRL1 of SEQ ID NO: 64 with substitution of 0, 1, 2, 3, 4, or 5 amino acids, a CDRL2 of SEQ ID NO: 65 with substitution of 0, 1, 2, 3, 4, or 5 amino acids, and a CDRL3 of SEQ ID NO: 66, and with substitution of 0, 1, 2, 3, 4, or 5 amino acids

c) the second binding part comprises a light chain constant region of human lambda type, and a light chain variable region of human lambda type, comprising as CDRL1, CDRL2 and CDRL3 a group of CDRs selected from the group consisting of I) CDRL1 of SEQ ID NO: 6, a CDRL2 of SEQ ID NO: 7 and a CDRL3 of SEQ ID NO: 8,

II) CDRL1 of SEQ ID NO: 10, a CDRL2 of SEQ ID NO: 11 and a CDRL3 of SEQ ID NO: 12,

III) CDRL1 of SEQ ID NO: 14, a CDRL2 of SEQ ID NO: 15 and a CDRL3 of SEQ ID NO: 16,

IV) CDRL1 of SEQ ID NO: 18, a CDRL2 of SEQ ID NO: 19 and a CDRL3 of SEQ ID NO: 20, and

V) CDRL1 of SEQ ID NO: 22, a CDRL2 of SEQ ID NO: 23 and a CDRL3 of SEQ ID NO: 24.

5 In one example embodiment the second binding part in c) comprises a light chain selected from the group consisting of SEQ ID NOs: 25, 26, 27, 28, and 29.

In one example embodiment, the bispecific antibody comprises a first binding part, specifically binding to human CEACAM5, and a second binding part, specifically binding to human CD3ε, wherein:

10 a) the first binding part comprises a heavy chain variable region (VH), which comprises a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b) the first binding part comprises a light chain variable region (VL) comprising a CDRL set in which the CDRL1 has the consensus sequence of SEQ ID NO: 136, the CDRL2 has the consensus sequence of SEQ ID NO: 137, and the CDRL3 has the consensus sequence of SEQ ID NO: 138, and

15 c) the second binding part comprises a VH comprising a CDRH1 of SEQ ID NO: 2, CDRH2 of SEQ ID NO: 3 and CDRH3 of SEQ ID NO: 4.

In one example embodiment the first binding part comprises as variable light chain framework sequence the framework sequence of SEQ ID NO: 31. In one example embodiment the first binding part comprises as variable light chain framework sequence the framework sequence of SEQ ID NO: 35. In one example embodiment the first binding part comprises as variable light chain framework sequence the framework sequence of SEQ ID NO: 59. In one example embodiment the first binding part comprises as variable light chain framework sequence the framework sequence of SEQ ID NO: 63.

25 In one example embodiment, the first binding part specifically binding to CEA, comprises as heavy chain variable region a heavy chain variable region of an amino acid sequence SEQ ID NO: 1 and as light chain variable region a light chain variable region of an amino acid sequence that is 98%, 99% or 100% identical to an amino acid sequence selected from the group of SEQ ID NO: 31 or
30 SEQ ID NO: 35, SEQ ID NO: 59 or SEQ ID NO: 63, and the second binding part specifically binding to CD3, comprises as heavy chain variable region a heavy chain variable region of amino acid sequence SEQ ID NO: 1 and as light chain variable region a light chain variable region of

amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 9, SEQ ID NO: 13, SEQ ID NO: 17, and SEQ ID NO: 21.

In one ~~example embodiment~~ the bispecific antibody according to the ~~invention-disclosure~~ is characterized in comprising a first binding part specific for CEA, comprising a kappa light chain variable domain and a kappa light chain constant domain and a second binding part specific for CD3ε, comprising a lambda light chain variable domain and a lambda light chain constant domain.

In one ~~example embodiment~~ the bispecific antibody according to the ~~invention-disclosure~~ is characterized in comprising a first binding part specific for CEA, comprising a lambda light chain variable domain and a kappa light chain constant domain and a second binding part specific for CD3ε, comprising a lambda light chain variable domain and a lambda light chain constant domain.

In one ~~example embodiment~~ the bispecific antibody according to the ~~invention-disclosure~~ is characterized in comprising a first binding part specific for CEA, comprising a lambda light chain variable domain and a lambda light chain constant domain and a second binding part specific for CD3ε, comprising a lambda light chain variable domain and a kappa light chain constant domain.

In a particular ~~example embodiment~~ the Fc domain exhibits reduced binding affinity to an Fc receptor and/or reduced effector function, as compared to a native/wild type IgG1 Fc domain. In certain ~~examples embodiments~~ the Fc domain is engineered to have reduced binding affinity to an Fc receptor and/or reduced effector function, as compared to a non-engineered Fc domain. In one ~~example embodiment~~, the Fc domain comprises one or more amino acid substitution that reduces binding to one or more Fc receptors and/or reduces effector functions. In one ~~example embodiment~~ such one or more substitutions are selected from the group consisting of Pro238, Asp265, Asp270, Asn297 (loss of Fc carbohydrate), Pro329, Leu234, Leu235, Gly236, Gly237, Ile253, Ser254, Lys288, Thr307, Gln311, Asn434, and His435 (Shields, R. L., et al., J. Biol. Chem. 276 (2001) 6591-6604; Lund, J., et al., FASEB J. 9 (1995) 115-119; Morgan, A., et al., Immunology 86 (1995) 319-324; EP 0 307 434). In one ~~example embodiment~~ the antibody is in regard to FcR binding of IgG4 subclass or of IgG1 or IgG2 subclass with a mutation in S228, L234, L235 and/or D265, and/or contains the PVA236 mutation. In one ~~example embodiment~~ the mutations in the Fc domain are S228P, L234A, L235A, L235E and/or PVA236. In another ~~example embodiment~~ the mutations in Fc domain are

in IgG4 S228P and in IgG1 L234A and L235A. In one ~~example~~embodiment, the one or more amino acid substitution in the Fc domain that reduces binding to one or more Fc receptors and/or reduces effector functions is at one or more position selected from the group of L234, L235, and P329 (Kabat EU index numbering). In particular ~~example~~embodiments, each subunit of the Fc domain comprises two amino acid substitutions that reduce binding to an Fc receptor and/or reduces effector function wherein said amino acid substitutions are L234A and L235A (Kabat EU index numbering). In particular ~~example~~embodiments, each subunit of the Fc domain comprises three amino acid substitutions that reduce binding to an Fc receptor and/or reduces effector function wherein said amino acid substitutions are L234A, L235A and P329A (Kabat EU index numbering). In one such ~~example~~embodiment, the Fc domain is an IgG1Fc domain, particularly a human IgG1Fc domain (Kabat EU index numbering). In one ~~example~~embodiment, the Fc domain is of IgG4 subclass and in one ~~example~~embodiment of IgG4 subclass with mutation S228P.

In one ~~example~~embodiment the Fc receptor is an Fcγ receptor. In one ~~example~~embodiment the Fc receptor is a human Fc receptor. In one ~~example~~embodiment, the Fc receptor is an activating Fc receptor. In a specific ~~example~~embodiment, the Fc receptor is human FcγRIIIA, FcγRI, and/or FcγRIIIA. In one ~~example~~embodiment, the effector function is antibody-dependent cell-mediated cytotoxicity (ADCC), but not limited to only ADCC.

An ~~example~~embodiment of the ~~invention~~disclosure is a kappa CL region of SEQ ID NO: 58 for use in the second binding part as CL region in the construction of a bispecific antibody comprising a common heavy chain of SEQ ID NOs: 43, 44, or 45, and a lambda CL region of SEQ ID NO: 41 as CL region in the first binding part.

An ~~embodiment~~example of the ~~invention~~disclosure is a kappa CL region of SEQ ID NO: 58 for use in the second binding part, specifically binding to CD3 as CL region in the construction of a bispecific antibody according to the ~~disclosure~~invention, comprising a common heavy chain of SEQ ID NOs: 43, 44, or 45, and a lambda CL region of SEQ ID NO: 41 as CL region in the first binding part, specifically binding to CEACAM5.

An ~~example~~embodiment of the ~~invention~~disclosure is a kappa CL region of SEQ ID NO: 58 for use in the second binding part, specifically binding to CD3 as CL region in the construction of a bispecific

antibody according to the ~~disclosure~~invention, comprising a common heavy chain of SEQ ID NOs: 43, 44, or 45, a variable light chain of SEQ ID NOs: 5, 9, 13, 17, or 21, and a lambda CL region of SEQ ID NO: 41 as CL region in the first binding part, specifically binding to CEACAM5.

A further ~~example embodiment~~ of the ~~invention~~disclosure is an oligonucleotide, selected from the group consisting of SEQ ID NOs: 76, 77, 78, and 79 for use in the antibody affinity maturation by oligonucleotide-directed mutagenesis using degenerated oligonucleotides of the respective light chain variable region of SEQ ID NOs: 31, 35, 59, and 63.

In another aspect ~~is provided the present disclosure refers to~~ a method of producing the bispecific of the invention, comprising the steps of a) culturing the host cell of the invention under conditions suitable for the expression of the bispecific antibody and b) recovering the bispecific antibody. The ~~invention~~disclosure also encompasses a bispecific antibody produced by the method of the ~~invention~~disclosure.

The ~~invention~~disclosure further provides a pharmaceutical composition comprising the bispecific antibody of the ~~disclosure~~invention and a pharmaceutically acceptable carrier. Also encompassed by the ~~invention~~disclosure are methods of using the bispecific antibody and pharmaceutical composition of the ~~disclosure~~invention. In one aspect the ~~invention~~disclosure provides a bispecific antibody or a pharmaceutical composition of the ~~invention~~disclosure for use as a medicament. In one aspect is provided a bispecific antibody or a pharmaceutical composition according to the ~~invention~~disclosure for use in the treatment of a disease in an individual in need thereof. In a specific ~~example embodiment~~ the disease is cancer.

Also provided is a bispecific antibody of the ~~invention~~disclosure for use in the manufacture of a medicament for the treatment of a disease in an individual in need thereof; 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 Bispecific antibody according to the ~~disclosure~~invention in a pharmaceutically acceptable form. In a specific ~~example embodiment~~ the disease is cancer. In any of the above ~~examples~~embodiments the individual preferably is a mammal, particularly a human.

The ~~invention~~disclosure also ~~provides~~describes a method for inducing lysis of a target cell, particularly a tumor cell, comprising contacting a target cell with a bispecific antibody of the ~~disclosure~~invention in the presence of a T cell, particularly a cytotoxic T cell.

A further ~~example embodiment~~ of the ~~invention-disclosure~~ is the bispecific antibody according to the ~~disclosure invention~~ for use in the manufacture of a medicament for treating a subject having a cancer that expresses CEA.

5 A further ~~example embodiment~~ of the ~~invention-disclosure~~ is the bispecific antibody according to the ~~invention-disclosure~~ for use in the manufacture of a medicament according to the ~~invention-disclosure~~, characterized in that the cancer is selected from the group consisting of colorectal cancer, non-small cell lung cancer (NSCLC), esophageal cancer, gastric/esophageal junction cancer, pancreatic cancer and breast cancer.

10 A further ~~example embodiment~~ of the ~~invention-disclosure~~ is a bispecific antibody according to the ~~invention-disclosure~~ for use in simultaneous, separate, or sequential combination with an anti-CD47 antibody. In one ~~example embodiment~~ the anti-CD47 antibody is Magrolimab, ALX148 or TTI-621 and/or TTI-622.

15 A further ~~example embodiment~~ of the ~~invention-disclosure~~ is a bispecific antibody according to the ~~invention-disclosure~~, for use in simultaneous, separate, or sequential combination with a second bispecific antibody comprising a third binding part specifically binding to human CEACAM5, and a fourth binding part specifically binding to human CD47 in the treatment of a subject having a cancer
20 that expresses CEA.

Such second bispecific CEACD47 antibodies are described in PCT/IB2019/054559 and US16/428,359.

25 A further ~~example embodiment~~ of the ~~invention-disclosure~~ is a bispecific antibody according to the ~~invention-disclosure~~ for use according to the ~~invention-disclosure~~, characterized in that the bispecific antibody according to the ~~disclosure invention~~ and the second bispecific CEACD47 antibody are administered to said subject alternately in 6 to 15 day intervals, but not limited to such intervals.

30 A further ~~example embodiment~~ of the ~~invention-disclosure~~ is a first bispecific antibody according to the ~~disclosure invention~~, comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3 according to the ~~invention-disclosure~~, and a second bispecific antibody CEACD47 for use in the treatment of cancer according to the ~~disclosure invention~~, characterized

in that said cancer is colorectal cancer, non-small cell lung cancer (NSCLC), gastric cancer, esophageal cancer, pancreatic cancer and breast cancer.

5 A further example embodiment of the ~~invention-disclosure~~ is a composition comprising a bispecific antibody according to the ~~invention-disclosure~~, characterized in not competing with said second CEAxCD47 bispecific antibody as defined above for use in the treatment of a subject having a cancer that expresses CEA.

10 A further example embodiment of the ~~invention-disclosure~~ is a method for the treatment of a human patient diagnosed with a tumor (cancer), especially a solid tumor, especially a solid cancer that expresses CEA, especially colorectal cancer, non-small cell lung cancer (NSCLC), gastric cancer, esophageal cancer, pancreatic cancer and breast cancer, comprising administering an effective amount of an bispecific antibody according to the disclosure ~~invention~~ and a second bispecific antibody as described in PCT/IB2019/054559 and US16/428,359, against CEA and CD47, to the
15 human patient, the method comprising subsequently:

administering to the patient a dose of 0.1 to 30 mg/kg, in a further example embodiment of 0.5 to 10 mg/kg, in a further example embodiment of 1 to 10 mg/kg of said second anti CEAxCD47 antibody, e.g. weekly over 4 to 12 weeks,

administering to the patient said second antibody q1, q2w, q3w or optionally q4w,

20 administering after these 4 to 12 weeks and after additional 2 or 3 or 4 elimination half-lives of said anti CEAxCD47 antibody to the patient a dose of 0.1 to 10 mg/kg of an antibody according to the disclosure ~~invention~~,

administering to the patient said antibody according to the disclosure ~~invention~~ q1, q2w, q3w or optionally q4w,

25 waiting 2 or 3 or 4 elimination half-lives of said antibody according to the disclosure ~~invention~~ and then

optionally repeating said cycle of CEA x CD47 bispecific antibody administration followed by CEA x CD3 bispecific antibody administration and optionally repeat again that cycle.

30 This “alternating” method is applied if the antibody of the ~~invention-disclosure~~ and the second bispecific antibody are competitive regarding binding to CEA.

In case said CEA x CD47 bispecific antibody and the CEA x CD3 bispecific antibody according to this disclosure invention are not competitive, the two bispecific antibodies can also be administered in a manner (“simultaneous manner”) that the patient experiences therapeutically effective plasma and tissue concentrations of both bispecific antibodies in parallel, e.g. by administration to the patient at about the same time a dose of 0.1 to 30 mg/kg, in a further example embodiment of 0.5 to 10 mg/kg, in a further example embodiment of 1 to 10 mg/kg of the CEA x CD47 bispecific antibody and 0.1 to 10 mg/kg of the CEA x CD3 bispecific antibody of this disclosure invention, followed by one or more of these combined administrations at a frequency of q1w or q2w or q3w or optionally q4w.

The term “q1w” means administration once a week; q2w means administration every two weeks etc.

~~A~~ In a further aspect, embodiment of the invention is the present disclosure refers to a pharmaceutical composition comprising an bispecific antibody according to the invention as disclosed herein and a pharmaceutically acceptable excipient or carrier.

~~In a~~ further preferred aspect embodiment of the invention the present disclosure refers to is a pharmaceutical composition comprising an antibody according to the invention as disclosed herein for use as a medicament.

A further preferred example embodiment of the invention disclosure is a pharmaceutical composition comprising an antibody according to the invention disclosure for use as a medicament in the treatment of solid tumor disorders expressing CEA.

A further preferred example embodiment of the invention disclosure is a pharmaceutical composition comprising an antibody according to the invention disclosure for use as a medicament in the treatment of colorectal cancer, NSCLC (non-small cell lung cancer), gastric cancer, esophageal cancer, pancreatic cancer or breast cancer.

A further ~~example embodiment~~ of the ~~invention~~ disclosure is a composition according to the ~~disclosure~~ invention, characterized in that the cancer is colorectal cancer, non-small cell lung cancer (NSCLC), gastric cancer, esophageal cancer, pancreatic cancer, or breast cancer.

5 A further ~~example embodiment~~ of the ~~invention~~ disclosure is an antibody according to the ~~disclosure~~ invention for use in the manufacture of a pharmaceutical composition.

A further ~~example embodiment~~ of the ~~invention~~ disclosure is an antibody according to the ~~invention~~ disclosure and a pharmaceutically acceptable excipient or carrier for use in the manufacture of a
10 pharmaceutical composition.

A further ~~example embodiment~~ of the ~~invention~~ disclosure is of an antibody according to the ~~disclosure~~ invention for use in the manufacture of a medicament in the treatment of solid tumor disorders.

15 A further ~~example embodiment~~ of the ~~invention~~ disclosure is of an antibody according to the ~~disclosure~~ invention for use in the treatment of colorectal cancer, NSCLC (non-small cell lung cancer), gastric cancer, esophageal cancer, pancreatic cancer or breast cancer.

Another ~~aspect example~~ of the ~~disclosure describes invention provides~~ a method of inducing cell lysis of a
20 tumor cell comprising contacting the tumor cell with the bispecific antibody of any of above described ~~examples~~ embodiments. In some ~~embodiments~~ examples, the tumor cell is a colorectal cancer cell, NSCLC (non-small cell lung cancer), gastric cancer cell, esophageal cancer cell, pancreatic cancer cell or breast cancer cell.

25 In one ~~embodiment~~ example, the cell lysis is induced by T-cell directed cellular cytotoxicity (TDCC).

Another ~~aspect example~~ of the ~~disclosure describes invention provides~~ a method of treating a subject having a cancer that expresses CEA, the method comprising administering to the subject a therapeutically effective amount of the bispecific antibody of any of above described ~~embodiments~~ examples.
30

Another ~~aspect example~~ of the ~~disclosure describes invention provides~~ a method of treating a subject having a cancer that expresses CEA, the method comprising administering to the subject a therapeutically effective amount of the bispecific antibody of any of above described ~~embodiments~~ examples in combination with a bispecific antibody binding to human CEA and human CD47. If the CEAXCD47 antibody and the
35 CEAXCD3 antibody are competing they will compete for the CEA receptors on the surface of the tumor cell and the receptor occupancy and efficacy for each combination partner depends on

their binding affinity and their plasma concentrations and is therefore difficult to predict and also variable over time if the concentrations of the two drugs have a different elimination half-life respectively clearance from the body. Therefore, competing CEAxCD3 and CEAxCD47 bispecific antibodies should be given sequentially (alternating). If the CEAxCD3 and CEAxCD47 bispecific antibodies are not or only minimally competing they can be not only given sequentially but also in parallel (simultaneously) which may well be an advantage because tumor cell killing via engagement of T-cells by the CEAxCD3 bispecific antibody and at the same time via engagement of macrophages by the CEAxCD47 bispecific antibody is expected to be additive or may be even synergistic, which means efficacy is increased if both drugs are given in parallel.

Another ~~aspect-example~~ of the ~~invention-provides~~disclosure describes a method of increasing progression free survival and/or overall survival time in a subject having a cancer that expresses CEA, said method comprising administering to said subject a therapeutically effective amount of the bispecific antibody of any of above described ~~examples~~embodiments. In one ~~embodiment~~example, the cancer is colorectal cancer, non-small cell lung cancer (NSCLC), gastric cancer, esophageal cancer, pancreatic cancer, breast cancer, head and neck carcinoma, uterine cancer, bladder cancer, or another cancer expressing CEA.

In certain ~~embodiments~~examples of these methods, the bispecific antibody is administered in combination with chemotherapy or radiation therapy. In one ~~example~~embodiment, the subject is a patient suffering from colorectal cancer or lung cancer or gastric cancer, esophageal cancer, or pancreatic cancer or breast cancer or another cancer expressing CEA.

In certain ~~embodiments~~examples of these methods, the bispecific antibody of the ~~disclosure invention~~ is administered to a patient in doses ranging from 0.1 to 100 mg/kg of body weight per day or per week in single or divided doses, or by continuous infusion. In certain ~~embodiments~~examples, the bispecific antibody of the ~~disclosure invention~~ is administered to a patient in doses ranging from 1 to 20 mg/kg.

Another ~~aspect-example~~ of the ~~disclosure describes~~invention provides a method of treating a subject having a cancer that expresses CEA, the method comprising administering to the subject a therapeutically effective amount of the bispecific antibody of any of above described ~~examples~~embodiments in combination with a bispecific antibody against human CEA and human CD47. In certain ~~embodiments~~examples of these methods, the bispecific antibody is administered in combination with a bispecific anti-CEAxCD47 antibody in simultaneous, separate, or sequential combination. In certain

~~examples~~~~embodiments~~ of these methods, the bispecific anti-CEAxCD47 antibody is administered in an alternating pattern with an antibody of the ~~disclosure~~~~invention~~, with intervals of 6 to 15 days between administrations of the antibody of the ~~disclosure~~~~invention~~ and a bispecific anti-CEAxCD47 antibody. In certain ~~embodiments~~~~examples~~, the anti-CEAxCD47 antibody is administered to a patient in doses ranging from 0.1 to 100 mg/kg of body weight per day or per week in single or divided doses, or by continuous infusion.

In certain ~~embodiments~~~~examples~~ of these methods, the bispecific antibody is administered in combination with a PD-1 axis antagonist in simultaneous, separate, or sequential combination. In certain ~~embodiments~~~~examples~~ of these methods, the bispecific antibody is administered in combination with a bispecific anti-CEAxCD47 antibody and a PD-1 axis antagonist in simultaneous, separate, or sequential combination. In certain ~~embodiments~~~~examples~~, the PD-1 axis antagonist is administered to a patient in doses ranging from 0.1 to 100 mg/kg of body weight per day or per week in single or divided doses, or by continuous infusion.

Another ~~aspect~~~~exampl~~ of the ~~disclosure~~~~describes~~~~invention~~~~provides~~ a method of increasing progression free survival time and/or overall survival time in a subject having a cancer that abnormally expresses CEA, said method comprising administering to said subject a therapeutically effective amount of the bispecific antibody of any of above described ~~examples~~~~embodiments~~. In one ~~example~~~~embodiment~~, the cancer is colorectal cancer, non-small cell lung cancer (NSCLC), gastric cancer, esophageal cancer, pancreatic cancer or breast cancer.

In certain ~~embodiments~~~~examples~~ of these methods, the bispecific antibody is administered in combination with chemotherapy or radiation therapy. In one ~~example~~~~embodiment~~, the subject is a cancer patient with colorectal cancer or lung cancer or gastric cancer esophageal cancer, or pancreatic cancer or breast cancer or another CEA expressing cancer.

Another ~~embodiment~~~~example~~ of the ~~disclosure~~~~describes~~~~invention~~~~provides~~ a bispecific antibody according to the ~~disclosure~~~~invention~~ for use in any of the above described methods of treatment. In one ~~embodiment~~~~example~~, the cancer is selected from the group consisting of colorectal cancer, non-small cell lung cancer (NSCLC), gastric cancer, esophageal cancer, pancreatic cancer and breast cancer.

Another ~~embodiment example~~ of the ~~disclosure describes invention~~ provides polynucleotides that encode the bispecific antibodies disclosed herein or a domain thereof (*e.g.*, a variable light chain region and/or variable heavy chain region) that immunospecifically binds to CEACAM5 or CD3ε. In certain aspects, provided herein are polynucleotides comprising a nucleotide sequence encoding the light chain or heavy chain of an antibody described herein. The polynucleotides can comprise nucleotide sequences encoding a heavy chain comprising the VHs or heavy chain CDRs of antibodies described herein. The polynucleotides can comprise nucleotide sequences encoding a light chain comprising the VLs or light chain CDRs of antibodies described herein.

Certain ~~embodiments examples~~ are vectors comprising the isolated polynucleotides disclosed herein. Certain other ~~embodiments examples~~ are cells comprising the isolated polynucleotides or vectors encoding the bispecific antibodies disclosed herein. In some ~~embodiments examples~~, the cell is selected from the group consisting of Streptomyces, yeast, CHO, YB/20, NS0, PER-C6, HEK-293T, NIH-3T3, HeLa, BHK, Hep G2, SP2/0, R1.1, B-W, L-M, COS 1, COS 7, BSC1, BSC40, BMT10 cell, plant cell, insect cell, and human cell in tissue culture.

Certain ~~embodiments examples~~ are methods of making the antibodies disclosed herein. In some ~~examples embodiments~~, the method of making an antibody comprises expressing the antibody using cells comprising the isolated polynucleotides or vectors encoding the bispecific antibodies disclosed herein. In some ~~examples embodiments~~, the method of making an antibody comprises culturing a cell containing an isolated polynucleotide or vector encoding the bispecific antibodies disclosed herein and isolating the antibody expressed therein.

Description of the Drawings

Figure 1: Epitope binning of the new CEA binders used in the kappa/lambda (KL) CEAxCD3 bispecific antibodies (details in Example 5c)

For the characterization of the new CEA binding antibodies of this invention a competitive immunoassay is used. A competitive blocking profile is created against antibodies all binding to CEACAM5 (CEA) and for which the binding epitope has already been published. SM3E, MEDI (=MEDI-565), SAR, T84.66, Labetuzumab and CH1A1A are such antibodies, for details of these antibodies and the assay see Example 5c.

CLAIMS

1. A bispecific antibody comprising a first binding part, specifically binding to human CEACAM5, and a second binding part, specifically binding to human CD3ε, wherein:

a) the first binding part comprises a heavy chain variable region (VH), which comprises a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b) the first binding part comprises a light chain variable region (VL) comprising a CDRL set selected from the group consisting of

b1) a CDRL1 of SEQ ID NO: 32, CDRL2 of SEQ ID NO: 33, and CDRL3 of SEQ ID NO: 34,

b2) a CDRL1 of SEQ ID NO: 81, CDRL2 of SEQ ID NO: 82, and CDRL3 of SEQ ID NO: 83,

b3) a CDRL1 of SEQ ID NO: 84, CDRL2 of SEQ ID NO: 85, and CDRL3 of SEQ ID NO: 86,

b4) a CDRL1 of SEQ ID NO: 87, CDRL2 of SEQ ID NO: 88, and CDRL3 of SEQ ID NO: 89,

b5) a CDRL1 of SEQ ID NO: 90, CDRL2 of SEQ ID NO: 91, and CDRL3 of SEQ ID NO: 92,

b6) a CDRL1 of SEQ ID NO: 93, CDRL2 of SEQ ID NO: 94, and CDRL3 of SEQ ID NO: 95,

b7) a CDRL1 of SEQ ID NO: 96, CDRL2 of SEQ ID NO: 97, and CDRL3 of SEQ ID NO: 98,

b8) a CDRL1 of SEQ ID NO: 99, CDRL2 of SEQ ID NO: 100, and CDRL3 of SEQ ID NO: 101,

b9) a CDRL1 of SEQ ID NO: 102, CDRL2 of SEQ ID NO: 103, and CDRL3 of SEQ ID NO: 104,

b10) a CDRL1 of SEQ ID NO: 105, CDRL2 of SEQ ID NO: 106, and CDRL3 of SEQ ID NO: 107,

b11) a CDRL1 of SEQ ID NO: 108, CDRL2 of SEQ ID NO: 109, and CDRL3 of SEQ ID NO: 110, and

b12) a CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, and CDRL3 of SEQ ID NO: 113,

- c) the second binding part comprises a VH comprising a CDRH1 of SEQ ID NO: 2, CDRH2 of SEQ ID NO: 3 and CDRH3 of SEQ ID NO: 4, and
- d) the second binding part comprises a VL comprising a CDRL1 of SEQ ID NO: 18, CDRL2 of SEQ ID NO: 19, and CDRL3 of SEQ ID NO: 20.

5

2. The bispecific antibody according to claim 1, characterized in that the first binding part comprises a light chain variable region comprising a CDRL set selected from the group consisting of

10

a1) a CDRL1 of SEQ ID NO: 90, CDRL2 of SEQ ID NO: 91, and CDRL3 of SEQ ID NO: 92,

a2) a CDRL1 of SEQ ID NO: 96, CDRL2 of SEQ ID NO: 97, and CDRL3 of SEQ ID NO: 98,

a3) a CDRL1 of SEQ ID NO: 99, CDRL2 of SEQ ID NO: 100, and CDRL3 of SEQ ID NO: 101,

15

a4) a CDRL1 of SEQ ID NO: 102, CDRL2 of SEQ ID NO: 103, and CDRL3 of SEQ ID NO: 104,

a5) a CDRL1 of SEQ ID NO: 105, CDRL2 of SEQ ID NO: 106, and CDRL3 of SEQ ID NO: 107, and

20

a6) a CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, and CDRL3 of SEQ ID NO: 113.

3. The bispecific antibody according to claim 1, wherein the first binding part comprises a light chain variable region comprising a CDRL set selected from the group consisting of

25

a1) a CDRL1 of SEQ ID NO: 90, CDRL2 of SEQ ID NO: 91, and CDRL3 of SEQ ID NO: 92,

a2) a CDRL1 of SEQ ID NO: 105, CDRL2 of SEQ ID NO: 106, and CDRL3 of SEQ ID NO: 107, and

a3) a CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, and CDRL3 of SEQ ID NO: 113.

30

4. The bispecific antibody according to claim 1, comprising

- a) in the first binding part a heavy chain variable region VH of SEQ ID NO: 1,

b) in the first binding part a light chain variable region VL selected from the group consisting of

- b1) a light chain variable region VL of SEQ ID NO: 31,
- b2) a light chain variable region VL of SEQ ID NO: 114,
- 5 b3) a light chain variable region VL of SEQ ID NO: 115,
- b4) a light chain variable region VL of SEQ ID NO: 116,
- b5) a light chain variable region VL of SEQ ID NO: 117,
- b6) a light chain variable region VL of SEQ ID NO: 118,
- b7) a light chain variable region VL of SEQ ID NO: 119,
- 10 b8) a light chain variable region VL of SEQ ID NO: 120,
- b9) a light chain variable region VL of SEQ ID NO: 121,
- b10) a light chain variable region VL of SEQ ID NO: 122,
- b11) a light chain variable region VL of SEQ ID NO: 123, and
- b12) a light chain variable region VL of SEQ ID NO: 124, and

15 c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light chain variable region VL of SEQ ID NO: 17.

5. The bispecific antibody according to claim 2, comprising

a) in the first binding part a heavy chain variable region VH of SEQ ID NO: 1,

20 b) in the first binding part a light chain variable region VL selected from the group consisting of

- b1) a light chain variable region VL of SEQ ID NO: 117,
- b2) a light chain variable region VL of SEQ ID NO: 119,
- b3) a light chain variable region VL of SEQ ID NO: 120,
- 25 b4) a light chain variable region VL of SEQ ID NO: 121,
- b5) a light chain variable region VL of SEQ ID NO: 122, and
- b6) a light chain variable region VL of SEQ ID NO: 124, and

c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light chain variable region VL of SEQ ID NO: 17.

30 6. The bispecific antibody according to claim 3, comprising

a) in the first binding part a heavy chain variable region VH of SEQ ID NO: 1,

b) in the first binding part a light chain variable region VL selected from the group consisting of

b1) a light chain variable region VL of SEQ ID NO: 117,

b1) a light chain variable region VL of SEQ ID NO: 122, and

5 b4) a light chain variable region VL of SEQ ID NO: 124, and

c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light chain variable region VL of SEQ ID NO: 17.

7. A bispecific antibody comprising a first binding part, specifically binding to human CEACAM5

10 and a second binding part, specifically binding to human CD3ε, said antibody comprising

a) in the first binding part a heavy chain variable region VH of SEQ ID NO: 1,

b) in the first binding part a light chain selected from the group consisting of

b1) the light chain of SEQ ID NO: 40

b2) the light chain of SEQ ID NO: 125,

15 b3) the light chain of SEQ ID NO: 126,

b4) the light chain of SEQ ID NO: 127,

b5) the light chain of SEQ ID NO: 128,

b6) the light chain of SEQ ID NO: 129,

b7) the light chain of SEQ ID NO: 130,

20 b8) the light chain of SEQ ID NO: 131

b9) the light chain of SEQ ID NO: 132,

b10) the light chain of SEQ ID NO: 133,

b11) the light chain of SEQ ID NO: 134, and

b12) the light chain of SEQ ID NO: 135, and

25 c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light chain of SEQ ID NO: 28.

8. The bispecific antibody according to any one of claims 1 to 7, characterized in comprising a common heavy chain selected from the group consisting of

30 a) the heavy chain of SEQ ID NO: 43,

b) the heavy chain of SEQ ID NO: 44, and

c) the heavy chain of SEQ ID NO: 45.

9. A bispecific antibody comprising a first binding part, specifically binding to human CEACAM5, and a second binding part, specifically binding to human CD3ε, said antibody comprising a common heavy chain of SEQ ID NO: 45 and in the second binding part a light chain of SEQ ID NO: 28 and in the first binding part a light chain of SEQ ID NO: 128.

10. A bispecific antibody comprising a first binding part, specifically binding to human CEACAM5, and a second binding part, specifically binding to human CD3ε, said antibody comprising a common heavy chain of SEQ ID NO: 45 and in the second binding part a light chain of SEQ ID NO: 28 and in the first binding part a light chain of SEQ ID NO: 133.

11. A bispecific antibody comprising a first binding part, specifically binding to human CEACAM5, and a second binding part, specifically binding to human CD3ε, said antibody comprising a common heavy chain of SEQ ID NO: 45 and in the second binding part a light chain of SEQ ID NO: 28 and in the first binding part a light chain of SEQ ID NO: 135.

12. ~~Use of a~~ A bispecific antibody ~~for use in the manufacture of a medicament for treatment of~~ treating cancer, characterized in comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3ε, and characterized in

- a) binding to MKN-45 cells with an EC50 value of 0.5 nM to 50 nM,
- b) killing MKN-45, HPAF-II, or LS174T cells in an assay containing human PBMC in a concentration dependent manner with an EC50 value of 0.01 to 10 nM,
- c) binding to CEACAM5 expressing PEAK cells, but not cross reacting with CEACAM8 expressing PEAK cells,
- d) that the EC50 value for killing in a TDCC assay using LS174T tumor cells as target cells is not increased by more than a factor 5 in presence of 1 µg/mL of sCEA.

13. ~~The bispecific antibody for~~ The use according to claim 12, wherein said antibody

- a) inhibits tumor growth in a HPAF-II model by 25% or more compared to the vehicle control group, and
- b) competes with an anti-CEA antibody, comprising as VL and VH domains VL and VH of SEQ ID NOs: 48 and 49, respectively (MEDI).

14. ~~The bispecific antibody for use according to claim 12 or 13, wherein each subunit of the Fc domain comprises the amino acid substitutions L234A, L235A and P329A (Kabat EU index numbering).~~

5

15. Use of The the bispecific antibody according to any one of claims 1 to 14 for use in the treatment of ~~in the manufacture of a medicament for treating~~ colorectal cancer, non-small cell lung cancer (NSCLC), gastric cancer, pancreatic cancer and/or breast cancer.

10 16. Use of The the bispecific antibody according to any one of claims 1 to 14 in the manufacture of a medicament for ~~for use in treating carcinomas in vivo.~~

15 17. The bispecific antibody according to any one of claims 1 to 14 for use in ~~administering to a human subject suffering from cancer a pharmaceutically effective amount of a composition~~ containing a bispecific antibody of the invention therapy.

20 18. Use of The the bispecific antibody according to any one of claims 1 to 14 for use in the treatment of ~~in the manufacture of a medicament for treating~~ colorectal carcinoma, esophageal cancer, pancreatic adenocarcinoma, gastric cancer, non-small cell lung cancer, breast cancer, head and neck carcinoma, uterine and bladder cancers.

19. Use of tThe bispecific antibody according to any one of claims 1 to 14 in the manufacture of a medicament for use in monotherapy for the treatment of CEA expressing solid tumors

25 20. Use of Tthe bispecific antibody according to any one of claims 1 to 14 in the manufacture of a first medicament and use of a bispecific anti-CEAxCD47 antibody in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination therapy to treat cancer ~~for use in the treatment of cancer in combination with a bispecific anti-CEAxCD47 antibody, wherein the first and second medicaments are to be administered in simultaneously,~~
30 separately, or sequentially combination.

21. Use of The the bispecific antibody according to any one of claims 1 to 14 in the manufacture of a first medicament and use of a bispecific anti-CEAxCD47 antibody and/or a PD-1 axis antagonist in the manufacture of a second medicament, wherein the first and the second medicament are to be used in combination therapy to treat cancer, for use in the treatment of cancer
5 in combination with a bispecific anti-CEAxCD47 antibody and/or a PD-1 axis antagonist wherein the first and second medicaments are to be administered simultaneously, separately, or sequentially combination.

22. Use of tThe bispecific antibody according to any one of claims 1 to 14 in the manufacture of a
10 first medicament and use of a PD-1 axis antagonist in the manufacture of a second medicament, wherein the first and the second medicament are to be used in combination therapy to treat for use in the treatment of cancer, in combination with a PD-1 axis antagonist wherein the first and the second medicaments are to be administered simultaneously, separately, or sequentially combination.

23. Use of Tthe bispecific antibody according to any one of claims 1 to 14 in the manufacture of a
15 first medicament and use of a bispecific anti-CEAxCD47 antibody in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination therapy to treat cancer, wherein the first and the second medicament are to be administered for use in
20 administering in alternating administration, in intervals of 6 to 15 days between administration of the antibody of the inventionfirst medicament and the bispecific anti-CEAxCD47 antibodysecond medicament in the treatment of cancer.

24. The bispecific antibody of claim 17 or the for use according to any one of claims 15 to 16 and
25 18 to 23, wherein the antibody of the invention is to be administered to a patient in doses ranging from 0.1 to 100 mg/kg of body weight per day or per week in single or divided doses, or by continuous infusion.

25. The bispecific antibody for use according to claim 23, characterized in that the antibody of the
30 invention is to be administered to a patient in doses ranging from 1 to 20 mg/kg.

26. The ~~bispecific antibody~~ for use according to any one of claims 20 or 21, characterized in that the anti-CEA $\times$ CD47 antibody is to be administered to a patient in doses ranging from 0.1 to 100 mg/kg of body weight per day or per week in single or divided doses, or by continuous infusion.

27. The ~~bispecific antibody~~ for use according to claim 22, wherein the PD-1 axis antagonist is to be administered to a patient in doses ranging from 0.1 to 100 mg/kg of body weight per day or per week in single or divided doses, or by continuous infusion.

28. A pharmaceutical composition comprising a bispecific antibody according to any one of claims 1 to 14 and a pharmaceutically acceptable carrier.

29. A bispecific antibody, comprising a first binding part, specifically binding to human CEACAM5, and a second binding part, specifically binding to human CD3 ϵ , wherein:

a) the first binding part and the second binding part comprise each as heavy chain a common heavy chain which comprises a variable region comprising a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b) the first binding part comprises

i) a lambda light chain constant region, and

ii) a light chain variable region comprising a CDRL1 derived from SEQ ID NO: 32 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides, a CDRL2, derived from SEQ ID NO: 33 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides, and a CDRL3, derived from SEQ ID NO: 34 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides, and

c) the second binding part comprises a light chain variable region, comprising a CDRL1 of SEQ ID NO: 18, a CDRL2 of SEQ ID NO: 19 and a CDRL3 of SEQ ID NO: 20, and

d) the second binding part comprises a light chain constant region of SEQ ID NO: 41.

30. The bispecific antibody according to claim 29, wherein the second binding part in c) comprises a light chain selected from the group consisting of SEQ ID NOs: 25, 26, 27, 28, and 29.

31. A bispecific antibody, comprising a first binding part, specifically binding to human CEACAM5, and a second binding part, specifically binding to human CD3 ϵ , comprising

a) in the first binding part a heavy chain variable region VH having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 1, comprising a CDR1 of SEQ ID NO: 2, a CDR2 of SEQ ID NO: 3, and a CDR3 of SEQ ID NO: 4, and

b) a light chain variable region VL selected from the group consisting of

- 5 b1) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 31 and comprising a CDRL1 of SEQ ID NO: 32, CDRL2 of SEQ ID NO: 33, and CDRL3 of SEQ ID NO: 34,
- b2) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 114 and comprising a CDRL1 of SEQ ID NO: 81, CDRL2 of SEQ ID NO: 82, and CDRL3 of SEQ ID NO: 83,
- 10 b3) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 115 and a CDRL1 of SEQ ID NO: 84, CDRL2 of SEQ ID NO: 85, and CDRL3 of SEQ ID NO: 86,
- b4) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 116 and a CDRL1 of SEQ ID NO: 87, CDRL2 of SEQ ID NO: 88, and CDRL3 of SEQ ID NO: 89,
- 15 b5) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 117 and a CDRL1 of SEQ ID NO: 90, CDRL2 of SEQ ID NO: 91, and CDRL3 of SEQ ID NO: 92,
- b6) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 118 and a CDRL1 of SEQ ID NO: 93, CDRL2 of SEQ ID NO: 94, and CDRL3 of SEQ ID NO: 95,
- 20 b7) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 119 and a CDRL1 of SEQ ID NO: 96, CDRL2 of SEQ ID NO: 97, and CDRL3 of SEQ ID NO: 98,
- 25 b8) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 120 and a CDRL1 of SEQ ID NO: 99, CDRL2 of SEQ ID NO: 100, and CDRL3 of SEQ ID NO: 101,
- b9) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 121 and a CDRL1 of SEQ ID NO: 102, CDRL2 of SEQ ID NO: 103, and CDRL3 of SEQ ID NO: 104,
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b10) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 122 and a CDRL1 of SEQ ID NO: 105, CDRL2 of SEQ ID NO: 106, and CDRL3 of SEQ ID NO: 107, and

b11) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 123 and a CDRL1 of SEQ ID NO: 108, CDRL2 of SEQ ID NO: 109, and CDRL3 of SEQ ID NO: 110, and

b12) a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 124 and a CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, and CDRL3 of SEQ ID NO: 113,

c) the second binding part a heavy chain variable region VH having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 1, comprising a CDR1 of SEQ ID NO: 2, a CDR2 of SEQ ID NO: 3, and a CDR3 of SEQ ID NO: 4, and a light chain variable region VL having 97%, 98%, 99%, or 100% amino acid identity to SEQ ID NO: 17, comprising a CDRL1 of SEQ ID NO: 18, CDRL2 of SEQ ID NO: 19, and CDRL3 of SEQ ID NO: 20.

32. The bispecific antibody according to any one of claims 29 to 31, wherein the common heavy chain is of SEQ ID NO: 43.

33. The bispecific antibody according to any one of claims 29 to 31, wherein the common heavy chain is of SEQ ID NO: 44.

34. The bispecific antibody according to any one of claims 29 to 31, wherein the common heavy chain is of SEQ ID NO: 45.

~~35. A method of treating cancer, comprising administering an effective amount of~~ Use of the bispecific antibody of any one of claims 1 to 11 or 29 to 34, or the pharmaceutical composition of claim 28, in the manufacture of a medicament for treating cancer in ~~to~~ a subject in need thereof.

36. The ~~method-use~~ use of claim 35, wherein the bispecific antibody binds to MKN-45 cells with an EC50 value of 0.5 nM to 50 nM.

37. The ~~method~~use of claim 35 or 36, wherein the bispecific antibody kills MKN-45, HPAF-II, or LS174T cells in an assay containing human PBMC in a concentration dependent manner with an EC50 value of 0.01 to 10 nM.

5 38. The ~~method~~use of any one of claims 35 to 37, wherein the bispecific antibody binds to CEACAM5 expressing PEAK cells, but does not cross react with CEACAM8 expressing PEAK cells.

39. The ~~method~~use of any one of claims 35 to 38, wherein the bispecific antibody's
10 EC50 value for killing in a TDCC assay using LS174T tumor cells as target cells is not increased by more than a factor 5 in the presence of 1 µg/mL of sCEA relative to the EC50 in the absence of sCEA.

40. The ~~method~~use of any one of claims 35 to 39, wherein the bispecific antibody inhibits tumor
15 growth in a HPAF-II model by 25% or more compared to the vehicle control group.

41. The ~~method~~use of any one of claims 35 to 40, wherein the bispecific antibody competes with
an anti-CEA antibody comprising as VL and VH the VL and VH of sequences SEQ ID NOs: 48
and 49.

20 42. The ~~method~~use of any one of claims 35 to 41, wherein the bispecific antibody comprises the amino acid substitutions L234A, L235A and P329A in each subunit of the Fc domain, as numbered according to Kabat EU index numbering.

25 43. The ~~method~~use of any one of claims 35 to 42, wherein the subject is a human.

44. The ~~method~~use of any one of claims 35 to 43, wherein the subject has colorectal cancer, non-small cell lung cancer (NSCLC), gastric cancer, pancreatic cancer or breast cancer.

30 45. The ~~method~~use of any one of claims 35 to 43, wherein the subject has a carcinoma.

46. The ~~method-use~~ of any one of claims 35 to 43, wherein the subject has colorectal carcinoma, esophageal cancer, pancreatic adenocarcinoma, gastric cancer, non-small cell lung cancer, breast cancer, head and neck carcinoma, uterine cancer, or bladder cancer.

5 47. The ~~method-use~~ of any one of claims 35 to 46, wherein the bispecific antibody is to be administered as a monotherapy

48. The ~~method-use~~ of claim 47, wherein the bispecific antibody is to be administered as a treatment of CEA-expressing solid tumors.

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49. The ~~method-use~~ of any one of claims 35 to 46, wherein the bispecific antibody is to be administered in combination with a bispecific anti-CEAxCD47 antibody in simultaneous, separate, or sequential combination.

15 50. The ~~method-use~~ of claim 49, wherein the bispecific antibody is to be administered in an alternating manner with a bispecific anti-CEAxCD47 antibody with intervals of 6 to 15 days between administration of the bispecific antibody of the invention and the bispecific anti-CEAxCD47 antibody.

20 51. The ~~method-use~~ of any one of claims 35 to 46, 49, or 50, wherein the bispecific antibody is to be administered in combination with a PD-1 axis antagonist in simultaneous, separate, or sequential combination.

25 52. The ~~method-use~~ of any one of claims 35 to 51, wherein the bispecific antibody is to be administered in a dose between 0.1 to 100 mg/kg of body weight per day or per week.

53. The ~~method-use~~ of any one of claims 35 to 52, wherein the bispecific antibody is to be administered in a dose between 1 to 20 mg/kg.

30 54. The ~~method-use~~ of claim 52 or 53, wherein the bispecific antibody is to be administered in a divided dose.

55. The ~~method~~-use of claim 52 or 53, wherein the bispecific antibody is to be administered by continuous infusion.

56. The ~~method~~-use of any one of claims 49-55, wherein the bispecific anti-CEA $\times$ CD47 antibody is to be administered to a patient in doses ranging from 0.1 to 100 mg/kg of body weight per day or per week in single or divided doses, or by continuous infusion.

57. The ~~method~~-use of any one of claims 51 to 56, wherein the PD-1 axis antagonist is to be administered to a patient in doses ranging from 0.1 to 100 mg/kg of body weight per day or per week in single or divided doses, or by continuous infusion.

58. An isolated polynucleotide that encodes the antibody of any one of claims 1 to 34, or a binding part thereof.

59. A vector comprising the isolated polynucleotide of claim 58.

60. A cell comprising the isolated polynucleotide of claim 58 or the vector of claim 59.

61. The cell of claim 60, which is selected from the group consisting of Streptomyces, yeast, CHO, YB/20, NS0, PER-C6, HEK-293T, NIH-3T3, HeLa, BHK, Hep G2, SP2/0, R1.1, B-W, L-M, COS 1, COS 7, BSC1, BSC40, BMT10 cell, plant cell, insect cell, and human cell in tissue culture.

62. A method of making a bispecific antibody, comprising expressing the bispecific antibody in the cell of claim claim 60 or 61.

63. A method of making a bispecific antibody, comprising culturing the cell of claim 60 or 61 and isolating the antibody expressed therein.