

Claims

1. A bispecific antibody comprising a first binding part specifically binding to human CEACAM5 and a second binding part specifically binding to human CD47 characterized in that:
 - a) the first binding part comprises as heavy chain variable region a heavy chain variable region comprising a CDRH1 of SEQ ID NO:1, a CDRH2 of SEQ ID NO:2 and a CDRH3 of SEQ ID NO:3,
 - 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:14, CDRL2 of SEQ ID NO:15, and CDRL3 of SEQ ID NO:16, or
 - b2) a CDRL1 of SEQ ID NO:17, CDRL2 of SEQ ID NO:18, and CDRL3 of SEQ ID NO:19,
 - b3) a CDRL1 of SEQ ID NO:20, CDRL2 of SEQ ID NO:21, and CDRL3 of SEQ ID NO:22,
 - b4) a CDRL1 of SEQ ID NO:23, CDRL2 of SEQ ID NO:24, and CDRL3 of SEQ ID NO:25, and
 - b5) a CDRL1 of SEQ ID NO:26, CDRL2 of SEQ ID NO:27, and CDRL3 of SEQ ID NO:28,
 - c) the second binding part comprises as heavy chain variable region a heavy chain variable region comprising a CDRH1 of SEQ ID NO:1, a CDRH2 of SEQ ID NO:2 and a CDRH3 of SEQ ID NO:3, and as light chain variable region a light chain variable region comprising a CDRL1 of SEQ ID NO:7, a CDRL2 of SEQ ID NO:8, and a CDRL3 of SEQ ID NO:9.
2. The bispecific antibody according to claim 1, characterized in comprising in the first binding part as variable heavy chain region a variable heavy chain region of SEQ ID NO:4 and as variable light chain region a variable light chain region selected from the group consisting of SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, and SEQ ID NO:36 and comprising in the second binding part as variable heavy chain region a variable heavy chain region of SEQ ID NO:4 and as variable light chain region a variable light chain region having of SEQ ID NO:10.
3. The bispecific antibody according to claim 1, characterized in comprising in the first binding part a heavy chain comprising SEQ ID NO:5 and a light chain selected from the group consisting of SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, and SEQ ID NO:41 and comprising in the second binding part a heavy chain region of SEQ ID NO:5 and a light chain having of SEQ ID NO:11.
4. The bispecific antibody according to any one of the preceding claims, characterized in comprising as heavy chain a common heavy chain of SEQ ID NO:6.
5. The bispecific antibody of any one of the preceding claims, wherein said antibody is monovalent for the first binding part and monovalent for the second binding part.
6. The bispecific antibody of any one of the preceding claims, wherein the constant and variable framework region sequences are human.

7. The bispecific antibody of any one of the preceding claims, wherein the light chain of the first binding part is a lambda light chain (VLCL) and the light chain of the second binding part is a kappa light chain (VKCK).
8. The bispecific antibody of any one of the preceding claims, wherein the antibody is human IgG1 type.
9. The bispecific antibody of any one of the preceding claims, wherein said antibody comprises a Fc region that has been glycoengineered to have a reduced number of fucose residues as compared to the same bispecific antibody that has not been glycoengineered.
10. The bispecific antibody of any one of the preceding claims, characterized in that said bispecific antibody competes for binding to CEACAM5 with anti-CEACAM5 antibody SM3E, which comprises the variable light and heavy chain regions of SEQ ID NO:43 and 44.
11. The bispecific antibody of any one of the preceding claims, characterized in binding to recombinant human CEACAM5 with a binding affinity (KD) of 2 to 10 nM.
12. The bispecific antibody of any one of the preceding claims, characterized in binding to human recombinant CD47 with a binding affinity of 100 nM to 600 nM.
13. The bispecific antibody of any one of the preceding claims, characterized by a ratio of the KD values for the binding to recombinant CEACAM3 and recombinant CEACAM5 of a factor of 100 or more.
14. The bispecific antibody of claim 13, characterized by a ratio of the KD values for the binding to recombinant CEACAM3 and recombinant CEACAM5 of a factor of between 100 and 200.
15. The bispecific antibody of any one of the preceding claims, characterized in an at least 8% increase in the maximum of phagocytosis index of LoVo tumor cells in comparison to the phagocytosis index of bispecific antibody K2AC22.
16. The bispecific antibody of claim 15, characterized in an increase in the maximum of phagocytosis index between 8% and 20% for LoVo tumor cells.
17. The bispecific antibody of any one of the preceding claims, characterized in an at least 8% increase in the maximum of phagocytosis index of Ls174T tumor cells in comparison to the phagocytosis index of K2AC22.
18. The bispecific antibody of claim 17, characterized in an increase in the maximum of phagocytosis index between 8% and 25% for Ls174T tumor cells.

19. The bispecific antibody of any one of the preceding claims, characterized in inhibiting the interaction between CD47 and SIRP α on MKN-45 cells with an IC₅₀ which is a factor of 10 or more lower than the IC₅₀ measured for K2AC22 under the same experimental conditions.
20. The bispecific antibody of claim 19, characterized in inhibiting the interaction between CD47 and SIRP α on MKN-45 cells with an IC₅₀ factor of between 10 and 30.
21. The bispecific antibody of any one of the preceding claims, characterized in inhibiting the interaction between CD47 and SIRP α on MKN-45 cells with an IC₅₀ of 0.1 nM or lower.
22. The bispecific antibody of claim 21, characterized in inhibiting the interaction between CD47 and SIRP α on MKN-45 cells with an IC₅₀ of 0.1 nM to 0.04 nM.
23. The bispecific antibodies of any one of the preceding claims, characterized in not competing for binding to CEACAM5 with cibisatamab.
24. The bispecific antibody of any one of the preceding claims, wherein said first bispecific antibody is characterized in that a second bispecific antibody, binding to human CEACAM5 and CD3 ϵ , in a concentration of 300 nM, does not shift the EC₅₀ of the binding curve of the first bispecific antibody to MKN-45 cells or to LS174T cells by more than a factor of 3 towards higher concentrations.
25. The bispecific antibody of claim 24, wherein said second bispecific antibody is TCB2014 or cibisatamab.
26. An isolated polynucleotide or set of polynucleotides encoding a bispecific antibody according to any one of the preceding claims.
27. An expression vector comprising the polynucleotide or polynucleotides of claim 26.
28. A host cell comprising the expression vector of claim 27.
29. A method for the production of a bispecific antibody according to any one of claims 1-25, comprising a) culturing a host cell of claim 28 under conditions which permit the production of said bispecific antibody, and b) isolating said antibody.
30. The bispecific antibody of any one of claims 1-25, for use in therapy of a human cancer.
31. A bispecific antibody for use according to claim 30, characterized in that the cancer is a solid cancer.
32. A bispecific antibody for use according to claim 30, characterized in that the cancer is a colorectal cancer, NSCLC (non-small cell lung cancer), gastric cancer, pancreatic cancer, breast cancer, or another CEACAM5 expressing cancer.

33. ~~Use of The the~~ bispecific antibody of any one of claims 1-25 ~~for use~~ in the manufacture of a medicament for treating a subject having a cancer that expresses CEACAM5.

34. ~~Use of Tthe~~ bispecific antibody of any one of claims 1-25 in the manufacture of a medicalment 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 CD3ε in the treatment of a subject having a cancer that expresses CEACAM5.

35. ~~Use of Tthe~~ bispecific antibody of any one of claims 1-25 ~~for use~~ in the manufacture of a medicament for use in simultaneous, separate, or sequential combination wherein the second bispecific antibody is TCB2014 or cibisatamab.

36. ~~The bispecific antibody for the use~~ according to claim 34 or 35, characterized in that the bispecific antibody ~~according to the invention~~ and the second bispecific antibody are to be administered to said subject simultaneously in 6 to 15 day intervals.

37. A pharmaceutical composition comprising a bispecific antibody of any one of claims 1-25 and a pharmaceutically acceptable excipient or carrier.

38. The pharmaceutical composition of claim 37, for use as a medicament.

39. The pharmaceutical composition of claim 37 or claim 38, for use as a medicament in the treatment of solid cancer.

40. The pharmaceutical composition of any one of claims 37-39, for use as a medicament in the treatment of colorectal cancer, NSCLC (non-small cell lung cancer), gastric cancer, pancreatic cancer, or breast cancer.

41. Use of the bispecific antibody of any one of claims 1-25 or the pharmaceutical composition of any one of claims 37-40 in the manufacture of a medicament for ~~A method of treating a subject having a cancer that expresses CEACAM5, the method comprising administering to the subject a therapeutically effective amount of the bispecific antibody of any one of claims 1-25 or the pharmaceutical composition of any one of claims 37-40.~~

42. ~~The method~~ use of claim 41, wherein the cancer is a human cancer.

43. ~~The method~~ use of claim 41 or 42, wherein the subject is a patient.

44. ~~The method~~ use of any one of claims 41-43, characterized in that the cancer is a colorectal cancer cell, NSCLC (non-small cell lung cancer) cell, gastric cancer cell, pancreatic cancer cell, breast cancer cell, or another tumor cell expressing CEACAM5.

45. The ~~method-use~~ of any one of claims 41-44, wherein the bispecific antibody is to be administered in combination with chemotherapy or radiation therapy.

46. Use of the CEACAM5 x CD47 bispecific antibody of any one of claims 1-25 and a second bispecific antibody against CEACAM5 and CD3 in the manufacture of a medicament for~~A method of treating a human patient with a tumor, comprising administering an effective amount of the CEACAM5 x CD47 bispecific antibody of any one of claims 1-25 and a second bispecific antibody against CEACAM5 and CD3.~~

47. The ~~method-use~~ of claim 46, wherein the CEACAM5 x CD47 bispecific antibody and the CEACAM5 and CD3 antibodies are not competitive.

48. The ~~method-use~~ of claim 46 or 47, wherein the antibodies are to be administered simultaneously.

49. The ~~method-use~~ of any one of claims 41 to 48, wherein the patient is to be administered one or more doses of 0.01 to 10 mg/kg of the bispecific antibody of any one of claims 1-25.

50. The ~~method-use~~ of any one of claims 46 to 48, wherein the patient is to be administered one or more doses of 0.01 to 10 mg/kg of the CEACAM5 x CD3 bispecific antibody and one or more doses of 1 to 20 mg/kg of the CEACAM5 x CD47 bispecific antibody.

51. The ~~method-use~~ of any one of claims 46-50, wherein the second antibody is TCB2014 or cibisatamab.

52. Use of the bispecific antibody of any one of claims 1-25 in the manufacture of a medicament for~~A method of increasing survival time in a subject having a cancer that expresses CEACAM5, said method comprising administering to said subject a therapeutically effective amount of the bispecific antibody of any one of claims 1-25.~~

53. The ~~method-use~~ of claim 52, characterized in that the cancer is colorectal cancer, non-small cell lung cancer (NSCLC), gastric cancer, pancreatic cancer, or breast cancer.

54. The ~~method-use~~ of any one of claims 52 or 53, wherein the bispecific antibody is to be administered in combination with chemotherapy and/or radiation therapy.

55. The ~~method-use~~ of any one of claims 52 to 54, wherein the patient is to be administered one or more doses of 0.01 to 10 mg/kg of the bispecific antibody of any one of claims 1-25.