

Claims

1. A bispecific antibody comprising a first antigen binding domain that specifically binds to programmed cell death protein 1 (PD1) and a second antigen binding domain that specifically binds to Lymphocyte activation gene-3 (LAG3), wherein
 - 5 said first antigen binding domain specifically binding to PD1 comprises a VH domain comprising
 - (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:1,
 - (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:2, and
 - (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:3; and
 - 10 a VL domain comprising
 - (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:4;
 - (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:5, and
 - (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:6; and
- said second antigen binding domain that specifically binds to LAG3 comprises
 - 15 a VH domain comprising
 - (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:14,
 - (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:15, and
 - (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:16; and
 - a VL domain comprising
 - 20 (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:17,
 - (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:18, and
 - (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19.
2. The bispecific antibody of claim 1, wherein the bispecific antibody comprises a Fc domain that is an IgG, particularly an IgG1 Fc domain or an IgG4 Fc domain and wherein the Fc
 - 25 domain comprises one or more amino acid substitution that reduces binding to an Fc receptor, in particular towards Fcγ receptor.
3. The bispecific antibody according to claims 1 or 2, wherein the first antigen-binding domain specifically binding to PD1 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 10.
- 30 4. The bispecific antibody according to any one of claims 1 to 3, wherein the second antigen-binding domain specifically binding to LAG3 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 20 and a VL domain comprising the amino acid sequence of SEQ ID NO: 21.

5. The bispecific antibody according any one of claims 1 to 4, wherein
- the first antigen binding domain specifically binding to PD1 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 10,
- 5 and the second antigen binding domain specifically binding to LAG3 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 20 and a VL domain comprising the amino acid sequence of SEQ ID NO: 21.
6. The bispecific antibody of any one of claims 1 to 5, wherein the bispecific antibody comprises an Fc domain of human IgG1 subclass with the amino acid mutations L234A, L235A and
- 10 P329G (numbering according to Kabat EU index).
7. The bispecific antibody of any one of claims 1 to 6, wherein the bispecific antibody comprises an Fc domain comprising a modification promoting the association of ~~the~~a first and a second subunit of the Fc domain.
8. The bispecific antibody of ~~any one of claims 1 to~~claim 7, wherein the first subunit of the Fc domain comprises the amino acid substitutions S354C and T366W (numbering according to Kabat EU index) and the second subunit of the Fc domain comprises the amino acid substitutions Y349C, T366S and Y407V (numbering according to Kabat EU index).
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9. The bispecific antibody of any one of claims 1 to 8, wherein the bispecific antibody comprises an Fc domain, a first Fab fragment comprising the antigen binding domain that specifically binds to PD1 and a second Fab fragment comprising the antigen binding domain that
- 20 specifically binds to LAG3.
10. The bispecific antibody of ~~any one of claims 1 to~~claim 9, wherein in ~~one of~~ the first or second Fab fragments ~~the~~ the variable domains VL and VH are replaced by each other so that the VH domain is part of the light chain and the VL domain is part of the heavy chain.
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11. The bispecific antibody of claim 9 or 10, wherein in the first Fab fragment comprising the antigen binding domain that specifically binds to PD1 the variable domains VL and VH are replaced by each other.
12. The bispecific antibody of any one of claims 1 to 11, wherein the bispecific antibody comprises a Fab fragment wherein in the constant domain CL the amino acid at position 124
- 30 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according

to Kabat EU Index), and in the constant domain CH1 the amino acids at positions 147 and 213 are substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to Kabat EU index).

13. The bispecific antibody of any one of claims 9 to 12, wherein in the second Fab fragment comprising the antigen binding domain that specifically binds to LAG3 the constant domain CL the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat EU Index), and in the constant domain CH1 the amino acids at positions 147 and 213 are substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to Kabat EU index).

14. The bispecific antibody of any one of claims 1 to 13, comprising a first heavy chain comprising an amino acid sequence of SEQ ID NO: 96, a first light chain comprising an amino acid sequence of SEQ ID NO: 98, a second heavy chain comprising an amino acid sequence of SEQ ID NO: 100, and a second light chain comprising an amino acid sequence of SEQ ID NO:101.

15. The bispecific antibody of any one of claims ~~1~~9 to 13, wherein the bispecific antibody comprises ~~a~~the second Fab fragment comprising the antigen binding domain that specifically binds to LAG3 which is fused to the C-terminus of the Fc domain.

16. The bispecific antibody of any one of claims 1 to 13 or 15, comprising a first heavy chain comprising an amino acid sequence of SEQ ID NO: 96, a first light chain comprising an amino acid sequence of SEQ ID NO: 98, a second heavy chain comprising an amino acid sequence of SEQ ID NO: 144, and a second light chain comprising an amino acid sequence of SEQ ID NO:101.

17. A polynucleotide encoding the bispecific antibody of any one of claims 1 to 16.

18. A prokaryotic or eukaryotic host cell comprising the polynucleotide according to claim 17.

19. A method of producing the bispecific antibody according to claims 1 to 16, comprising culturing the host cell of claim 18 under conditions suitable for the expression of the bispecific antibody and recovering the bispecific antibody from the culture.

20. A pharmaceutical composition comprising the bispecific antibody according to any one of claims 1 to 16 and at least one pharmaceutically acceptable excipient.

21. The bispecific antibody according to any one of claims 1 to 16 or the pharmaceutical composition according to claim 20 for use as a medicament.

22. The bispecific antibody according to any one of claims 1 to 16 or the pharmaceutical composition according to claim 20 for use in the treatment of cancer.

5 23. The bispecific antibody according to any one of claims 1 to 16 or the pharmaceutical composition according to claim 20 for use in the treatment of a chronic viral infection.

24. The bispecific antibody according to any one of claims 1 to 16 or the pharmaceutical composition according to claim 20 for use in the treatment of cancer, wherein the bispecific antibody is to be administered in combination with a chemotherapeutic agent, radiation and/
10 or other agents for use in cancer immunotherapy.

25. The bispecific antibody according to any one of claims 1 to 16 or the pharmaceutical composition according to claim 20 for use in the treatment of cancer, wherein the bispecific antibody is to be administered in combination with an anti-CEA/anti-CD3 bispecific antibody.