

The disclosure provides 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

said first antigen binding domain specifically binding to PD1 comprises

- 5 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
- a VL domain comprising
 - 10 (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.

In one aspect, the disclosure provides a bispecific antibody comprising a first antigen binding domain that specifically binds to programmed cell death protein 1 (PD1) and a second
15 antigen binding domain that specifically binds to Lymphocyte activation gene-3 (LAG3), wherein

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,
 - 20 (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
- 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
 - 25 (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

- 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
 - 30 (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:16; and

a VL domain comprising

- (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.

5 In particular, provided is 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 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 domain comprises one or more amino acid substitution that reduces
10 binding to an Fc receptor, in particular towards Fc γ receptor.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, wherein the second antigen binding domain that specifically binds to LAG3 comprises

(a) a VH domain comprising

- 15 (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
 (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:17,
20 (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; or

(b) a VH domain comprising

- (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:22,
 (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:23, and
25 (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:24; and
 a VL domain comprising

- v) in delaying progression of cancer,
- vi) in prolonging the survival of a patient suffering from cancer.

5 There is provided the bispecific antibody comprising a first antigen binding domain that
specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3
as described herein, or the pharmaceutical composition comprising the bispecific antibody, for
use in the treatment of a disease in an individual in need thereof. In a specific example, the
disclosure provides a bispecific antibody comprising a first antigen binding domain that
specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3,
10 or the pharmaceutical composition comprising the bispecific antibody, for use in the treatment of
cancer. In a further specific example, a bispecific antibody comprising a first antigen

binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, or the pharmaceutical composition comprising the bispecific antibody, for use in the modulation of immune responses is provided. In another example, a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and
5 a second antigen binding domain that specifically binds to LAG3, or a pharmaceutical composition comprising the bispecific antibody for use in the treatment of a chronic viral infection is provided.

In another aspect, there is provided the bispecific antibody as described herein before or the pharmaceutical composition as described herein before for use in the treatment of cancer.

10 In another aspect, there is provided the bispecific antibody as described herein before or the pharmaceutical composition as described herein before for use in the treatment of a chronic viral infection.

In another aspect, there is provided the bispecific antibody as described herein before or the pharmaceutical composition as described herein before for use in the treatment of cancer,
15 wherein the bispecific antibody is to be administered in combination with a chemotherapeutic agent, radiation and/ or other agents for use in cancer immunotherapy.

In another aspect, there is provided the bispecific antibody as described herein before or the pharmaceutical composition as described herein before for use in the treatment of cancer, wherein the bispecific antibody is to be administered in combination with an anti-CEA/anti-CD3
20 bispecific antibody.

The disclosure also provides a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein, or a pharmaceutical composition comprising the bispecific antibody for use in the prevention or treatment of cancer, wherein the bispecific antibody is
25 administered in combination with a chemotherapeutic agent, radiation and/or other agents for use in cancer immunotherapy. In a particular example, provided is bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein, or a pharmaceutical composition comprising the bispecific antibody for use in the prevention or treatment of cancer, wherein the bispecific
30 antibody is administered in combination with an anti-CEA/anti-CD3 bispecific antibody.

Also provided is the use of the bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein for the manufacture of a medicament for the treatment of a disease in an individual in need thereof, in particular for the manufacture of a medicament for the treatment of cancer, as well as a method of treating a disease in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein in a pharmaceutically acceptable form.

In a specific example, the disease is cancer. In another specific example, the disease is a chronic viral infection. In another example, a method of modulating of immune responses in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising the bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein in a pharmaceutically acceptable form is provided. In any of the above examples the individual is preferably a mammal, particularly a human.

The disclosure also provides a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein, or a pharmaceutical composition comprising the bispecific

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 first and second
subunit of the Fc domain.
8. The bispecific antibody of any one of claims 1 to 7, wherein the first subunit of the Fc domain
15 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).
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
20 binds to PD1 and a second Fab fragment comprising the antigen binding domain that
specifically binds to LAG3.
10. The bispecific antibody of any one of claims 1 to 9, wherein in one of the 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.
- 25 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).

- 5 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).
- 10 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 15. The bispecific antibody of any one of claims 1 to 13, wherein the bispecific antibody comprises a second Fab fragment comprising the antigen binding domain that specifically binds to LAG3 which is fused to the C-terminus of the Fc domain.
- 20 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.
- 25 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.