

Claims

1. An isolated antagonistic antibody or an antigen-binding portion thereof specifically binding PD-1, comprising a heavy chain complementarity determining region (HCDR)-1 a HCDR2 and a HCDR3 of SEQ ID NOs: 10, 14 and 17, respectively, and a light chain complementarity determining region (LCDR)-1 , a LCDR2 and a LCDR3 of SEQ ID NOs: 23, 26 and 32, respectively.
2. The antibody or the antigen-binding portion thereof of claim 1, comprising a heavy chain variable region (VH) of SEQ ID NO: 48 and a light chain variable region (VL) of SEQ ID NO: 56.
3. The antibody or the antigen-binding portion thereof of claim 1, wherein the antibody is human or humanized.
4. The antibody or the antigen-binding portion thereof of claim 3, wherein the antibody is
 - a) an IgG1 isotype, optionally comprising one, two, three, four, five, six, seven, eight, nine or ten substitutions in an Fc region;
 - b) an IgG2 isotype, optionally comprising one, two, three, four, five, six, seven, eight, nine or ten substitutions in the Fc region;
 - c) an IgG3 isotype, optionally comprising one, two, three, four, five, six, seven, eight, nine or ten substitutions in the Fc region;
 - d) an IgG4 isotype, optionally comprising one, two, three, four, five, six, seven, eight, nine or ten substitutions in the Fc region;
 - e) an IgG1 isotype comprising L234A, L235A, G237A, P238S, H268A, A330S and P331S substitutions;
 - f) an IgG2 isotype comprising V234A, G237A, P238S, H268A, V309L, A330S and P331S substitutions;
 - g) an IgG4 isotype comprising F234A, L235A, G237A, P238S and Q268A substitutions;
 - h) an IgG1 isotype comprising L234A, L235A or L234A and L235A substitutions;
 - i) an IgG4 isotype comprising F234A, L235A or F234A and L235A substitutions;
 - j) an IgG2 isotype comprising a V234A substitution;
 - k) an IgG4 isotype comprising a S228P substitution; or

- l) an IgG4 isotype comprising S228P, F234A and L235A substitutions, wherein residue numbering is according to the EU Index.
5. The antibody or the antigen-binding portion thereof of claim 2, comprising a heavy chain (HC) of SEQ ID NO: 72 and a light chain (LC) of SEQ ID NO: 73.
6. The antibody or the antigen-binding portion thereof of claim 2, wherein the antibody is a bispecific antibody, optionally binding PD-L1 (SEQ ID NO: 5), PD-L2 (SEQ ID NO: 8), LAG-3 (SEQ ID NO: 293), TIM-3 (SEQ ID NO: 138), CEACAM-1 (SEQ ID NO: 296), CEACAM-5 (SEQ ID NO: 307), OX-40 (SEQ ID NO: 279), GITR (SEQ ID NO: 271), CD27 (SEQ ID NO: 280), VISTA (SEQ ID NO: 286), CD137 (SEQ ID NO: 281), TIGIT (SEQ ID NO: 301) or CTLA-4 (SEQ ID NO: 292).
7. A pharmaceutical composition comprising the antibody or the antigen-binding portion thereof of claim 2 and a pharmaceutically accepted carrier.
8. An isolated antagonistic antibody specifically binding PD-1 or an antigen-binding portion thereof, comprising
- a) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 66, 67, 68, 69, 70 and 71, respectively;
 - b) the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65; and/or
 - c) the HC of SEQ ID NO: 74 and the LC of SEQ ID NO: 75.
9. A pharmaceutical composition comprising the antibody or the antigen-binding portion thereof of claim 8 and a pharmaceutically accepted carrier.
10. A kit comprising the antibody of claim 2.
11. The antibody or the antigen-binding portion thereof of claim 6, wherein the bispecific antibody comprises a first domain specifically binding PD-1 and a second domain specifically binding TIM-3.
12. The antibody or the antigen-binding portion thereof of claim 11, wherein

- a) the first domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 10, 14, 17, 23, 26 and 32, respectively or SEQ ID NOs: 66, 67, 68, 69, 70 and 71, respectively; and
- b) the second domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 97, 105, 115, 124, 133 and 143, respectively; or SEQ ID NOs: 91, 99, 108, 118, 127 and 136, respectively.

13. The antibody or the antigen-binding portion thereof of claim 12, wherein the bispecific antibody binds TIM-3 within TIM-3 residues 32-47 (WGKGACPVFECGNVVL) (SEQ ID NO: 261), optionally further binding within TIM-3 residues 50-56 (DERDVNY) (SEQ ID NO: 262).

14. The antibody or the antigen-binding portion thereof of claim 13, wherein

- a. the first domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 10, 14, 17, 23, 26 and 32, respectively, and the second domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 91, 99, 108, 118, 127 and 136, respectively;
- b. the first domain comprises the VH of SEQ ID NO: 48 and the VL of SEQ ID NO: 56, and the second domain comprises the VH of SEQ ID NO: 146 and the VL of SEQ ID NO: 156;
- c. the antibody comprises a first heavy chain (HC1), a first light chain (LC1), a second heavy chain (HC2) and a second light chain (LC2) of SEQ ID NOs: 186, 188, 191 and 194, respectively;
- d. the antibody comprises the HC1, the LC1, the HC2 and the LC2 of SEQ ID NOs: 186, 188, 248 and 194, respectively;
- e. the antibody comprises the HC1, the LC1, the HC2 and the LC2 of SEQ ID NOs: 241, 188, 245 and 194, respectively; and/or
- f. the antibody comprises the HC1, the LC1, the HC2 and the LC2 of SEQ ID NOs: 243, 188, 246 and 194, respectively.

15. The antibody or the antigen-binding portion thereof of claim 12, wherein the bispecific antibody binds TIM-3 within TIM-3 residues 90-102 (RIQIPGIMNDEKF) (SEQ ID NO: 263), optionally further binding within TIM-3 residues 50-56 (DERDVNY) (SEQ ID NO: 262).

16. The antibody or the antigen-binding portion thereof of claim 15, wherein

- a. the first domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 10, 14, 17, 23, 26 and 32, respectively, and the second domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 97, 105, 115, 124, 133 and 143, respectively;
- b. the first domain comprises the VH of SEQ ID NO: 48 and the VL of SEQ ID NO: 56, and the second domain comprises the VH of SEQ ID NO: 172 and the VL of SEQ ID NO: 173;
- c. the antibody comprises a HC1, a LC1, a HC2 and a LC2 of SEQ ID NOs: 186, 188, 192 and 195, respectively;
- d. the antibody comprises the HC1, the LC1, the HC2 and the LC2 of SEQ ID NOs: 241, 188, 244 and 195, respectively; and/or
- e. the antibody comprises the HC1, the LC1, the HC2 and the LC2 of SEQ ID NOs: 243, 188, 247 and 195, respectively.

17. The antibody or the antigen-binding portion thereof of claim 11, wherein the bispecific antibody is

- a. an IgG1 isotype, optionally comprising one, two, three, four, five, six, seven, eight, nine or ten substitutions in an Fc region;
- b. an IgG2 isotype, optionally comprising one, two, three, four, five, six, seven, eight, nine or ten substitutions in an Fc region;
- c. an IgG3 isotype, optionally comprising one, two, three, four, five, six, seven, eight, nine or ten substitutions in an Fc region;
- d. an IgG4 isotype, optionally comprising one, two, three, four, five, six, seven, eight, nine or ten substitutions in an Fc region;
- e. an IgG1 isotype comprising L234A, L235A, G237A, P238S, H268A, A330S and P331S substitutions;
- f. an IgG2 isotype comprising V234A, G237A, P238S, H268A, V309L, A330S and P331S substitutions;
- g. an IgG4 isotype comprising F234A, L235A, G237A, P238S and Q268A substitutions;
- h. an IgG1 isotype comprising L234A, L235A or L234A and L235A substitutions;
- i. an IgG4 isotype comprising F234A, L235A or F234A and L235A substitutions;
- j. an IgG2 isotype comprising a V234A substitution;
- k. an IgG4 isotype comprising a S228P substitution;
- l. an IgG4 isotype comprising S228P, F234A and L235A substitutions;
- m. an IgG2 isotype comprising F405L and R409K substitutions; or

- n. an IgG1 isotype comprising F405L and K409R substitutions, wherein residue numbering is according to the EU Index.

18. A pharmaceutical composition comprising the bispecific antibody of claim 12 and a pharmaceutically accepted carrier.

19. An isolated antagonistic antibody specifically binding PD-1 or an antigen-binding portion thereof, comprising a HCDR1, a HCDR2 and a HCDR3 of SEQ ID NOs: 11, 15 and 18, respectively and a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 20, 30 and 32, respectively.

20. The antibody or the antigen-binding portion thereof of claim 19, comprising a VH and a VL of SEQ ID NOs: 45 and 60, respectively.

21. The antibody or the antigen-binding portion thereof of claim 20, wherein the antibody is an IgG4 isotype comprising a S228P substitution.