

Patent Claims

1. An isolated antibody that binds to human PD1, wherein the antibody binds to the (core) sugar chain at Asn58 of glycosylated human PD1 of SEQ ID NO: 70 which is glycosylated at Asn58.
- 5 2. The antibody according to claim 1 wherein the antibody binds additionally to one or more amino acids of positions 60 to 64, 68, 78 to 84, 126 to 134 of human PD1.
3. The antibody according to any one of claims 1 or 2, wherein the antibody binds with its heavy chain to the the sugar chain at Asn58.
- 10 4. The antibody according to any one of claims 2 to 3, wherein the antibody binds to one or more amino acids of positions 61, 62, 64, 83, 126, 128, 132, 134 of human PD1.
5. The antibody according to any one of claims 2 to 3, wherein the antibody binds to amino acids of positions 61, 62, 64, 83, 126, 128, 132, 134 of human PD1.
- 15 6. The antibody according to any one of claims 2 to 3, wherein the antibody binds to acids of positions 60, 61, 62, 63, 64, 68, 78, 82, 83, 84, 126, 127, 128, 130, 131, 132, 133, 134 of human PD1.
7. The antibody according to any one of claims 1 to 6, wherein the antibody binds to human PD1, wherein the antibody binds to the first and second GlNAc, FUC, BMA and MAN within the (core) sugar chain at Asn58 of glycosylated human PD1 of SEQ ID NO: 70, which is glycosylated at Asn58.
- 20 8. The antibody according to any one of claims 1 to 7, wherein the antibody shows reduced binding to human PD1 of SEQ ID NO: 70 which is not glycosylated at Asn58 compared to the binding to human PD1 which is glycosylated at Asn58.
- 25 9. An isolated antibody that binds to human PD1, wherein the antibody comprises
 - (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:71; (b)
 - 30 HVR-H2 comprising the amino acid sequence of SEQ ID NO:72; (c) HVR-

5 H3 comprising the amino acid sequence of SEQ ID NO:73; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:74; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:75; (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:76, and (g) FR-H3 comprising the amino acid sequence of SEQ ID NO: 77 (of RDN) at positions of 71, 72 and 73 according to Kabat numbering

10. The isolated antibody that binds to human PD1 according to claim 9, wherein the antibody

A)

10 i) comprises a VH sequence of SEQ ID NO:7 and a VL sequence of SEQ ID NO:8;

ii) or humanized variant of the VH and VL of the antibody under i);

or B)

15 i) comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:58.

ii) comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:59.

iii) comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:60.

20 iv) comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:61.

11. An isolated antibody that binds to human PD1, wherein the antibody comprises

25 A) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:1; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:2; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:3; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:4; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:5; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:6; or

- 5 B) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:9; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:10; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:11; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:12; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:13; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:14; or
- 10 C) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:17; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:18; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:19; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:20; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:21; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:22; or
- 15 D) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:25; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:26; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:27; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:28; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:29; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:30; or
- 20 E) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:33; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:34; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:35; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:36; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:37; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:38; or
- 25 F) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:41; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:42; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:43; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:44; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:45; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:46; or
- 30 G) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:49; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:50; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:51; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:52; (e) HVR-L2

comprising the amino acid sequence of SEQ ID NO:53; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:54.

12. An isolated antibody that binds to human PD1, wherein the antibody comprises

- 5 A) (a) 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 selected from SEQ ID NO:3; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:4; (ii) HVR-L2
10 comprising the amino acid sequence of SEQ ID NO:5 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:6; or
- B) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:9, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:10, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:11; and (b) a VL domain comprising (i) HVR-L1
15 comprising the amino acid sequence of SEQ ID NO:12; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:13 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:14; or
- C) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:17, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:18, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:19; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:20; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:21 and (iii) HVR-L3
20 comprising the amino acid sequence of SEQ ID NO:22; or.
- D) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:26, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:27; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:28; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:29 and (iii) HVR-L3
30 comprising the amino acid sequence of SEQ ID NO:30; or

- 5 E) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:33, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:34, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:35; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:36; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:37 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:38; or
- 10 F) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:41, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:42, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:43; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:44; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:45 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:46; or
- 15 G) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:49, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:50, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:51; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:52; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:53 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:54.
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13. An isolated antibody that binds to human PD1, wherein the antibody
- A)
- 25 i) comprises a VH sequence of SEQ ID NO:7 and a VL sequence of SEQ ID NO:8;
- ii) or humanized variant of the VH and VL of the antibody under i);
- or B)
- i) comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:58.
- 30 ii) comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:59.

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iii) comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:60.

iv) comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:61.

5 or C)

i) comprises a VH sequence of SEQ ID NO:15 and a VL sequence of SEQ ID NO:16;

ii) or humanized variant of the VH and VL of the antibody under i);

or D)

10 i) comprises a VH sequence of SEQ ID NO:23 and a VL sequence of SEQ ID NO:24;

ii) or humanized variant of the VH and VL of the antibody under i);

or E)

15 i) comprises a VH sequence of SEQ ID NO:31 and a VL sequence of SEQ ID NO:32;

ii) or humanized variant of the VH and VL of the antibody under i);

or F)

i) comprises a VH sequence of SEQ ID NO:39 and a VL sequence of SEQ ID NO:40;

20 ii) or humanized variant of the VH and VL of the antibody under i);

or G)

i) comprises a VH sequence of SEQ ID NO:47 and a VL sequence of SEQ ID NO:48;

ii) or humanized variant of the VH and VL of the antibody under i);

or H)

- i) comprises a VH sequence of SEQ ID NO:55 and a VL sequence of SEQ ID NO:56;
 - ii) or humanized variant of the VH and VL of the antibody under i).
- 5 14. An isolated antibody that binds to human PD1, wherein the antibody
 - i) comprises a VH sequence of SEQ ID NO:7 and a VL sequence of SEQ ID NO:8;
 - ii) or humanized variant of the VH and VL of the antibody under i);
- 10 15. An isolated antibody that binds to human PD1, wherein the antibody comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:58.
- 16. An isolated antibody that binds to human PD1, wherein the antibody comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:59.
- 15 17. An isolated antibody that binds to human PD1, wherein the antibody comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:60.
- 18. An isolated antibody that binds to human PD1, wherein the antibody comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:61.
- 20 19. The anti-PD1 antibody according to any one of the preceding embodiments wherein the antibody is characterized independently by one or more of the following properties: the anti-PD-1 antibody
 - 25 i) competes for binding to PD-1 with an anti-PD-1 antibody comprising the VH with the amino acid sequence of SEQ ID NO:7 and VL with the amino acid sequence of SEQ ID NO:8, and/ or
 - ii) binds to a human and cynomolgus PD-1; and/ or

- iii) enhances the interferon-gamma (IFN-gamma) secretion by allogenic stimulated T cells by 85% or more at an antibody concentration of 10µg/ml; and/ or
- iv) enhances the tumor necrosis factor alpha (TNF alpha) secretion by allogenic stimulated T cells by 200% or more at an antibody concentration of 10µg/ml.
20. An isolated antibody that binds to PD1, wherein the antibody enhances the tumor necrosis factor alpha (TNF alpha) secretion by allogenic stimulated T cells by 200% or more at an antibody concentration of 10µg/ml in a Mixed lymphocyte reaction (MLR) assay.
21. An isolated antibody that binds to PD1, wherein the antibody enhances the interferon-gamma (IFN-gamma) secretion by allogenic stimulated T cells by 85% or more at an antibody concentration of 10µg/ml in a Mixed lymphocyte reaction (MLR) assay.
22. An isolated antibody that binds to human PD-1, wherein the antibody:
- i) competes for binding to PD-1 with an anti-PD1 antibody comprising the VH with the amino acid sequence of SEQ ID NO:7 and VL with the amino acid sequence of SEQ ID NO:8, and/ or
- ii) binds to a human and cynomolgus PD-1; and
- iii) enhances the interferon-gamma (IFN-gamma) secretion by allogenic stimulated T cells by 85% or more at an antibody concentration of 10µg/ml; and
- iv) enhances the tumor necrosis factor alpha (TNF alpha) secretion by allogenic stimulated T cells by 200% or more at an antibody concentration of 10µg/ml.
23. The antibody of according to any one of the preceding claims, which is a full length IgG1 antibody with mutations L234A, L235A and P329G (numbering according to the EU index of Kabat)
24. Isolated nucleic acid encoding the antibody according to any one of the preceding claims.

25. A host cell comprising the nucleic acid of claim 19.
26. A method of producing an antibody comprising culturing the host cell of claim 25 so that the antibody is produced.
- 5 27. The method of claim 26, further comprising recovering the antibody from the host cell.
28. A pharmaceutical formulation comprising the antibody according any one of claims 1 to 22 and a pharmaceutically acceptable carrier.
29. The antibody according any one of claims 1 to 22 for use as a medicament.
30. The antibody according any one of claims 1 to 22 for use in treating cancer.
- 10 31. Use of the antibody according any one of claims 1 to 22 in the manufacture of a medicament.
32. The use of claim 31, wherein the medicament is for treatment of cancer.
33. A method of treating an individual having cancer comprising administering to the individual an effective amount of the antibody of claim 1.