

CLAIMS

1. An anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody or antigen-binding portion comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

(a) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSEKYYVDSVKG (SEQ ID NO: 39) and HCDR3 of QLYGFDY (SEQ ID NO: 40); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQS (SEQ ID NO: 42) and LCDR3 of QQSYSTPWT (SEQ ID NO: 43);

(b) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSEKYYVDSVKG (SEQ ID NO: 39) and HCDR3 of QVYYFDY (SEQ ID NO: 44); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQS (SEQ ID NO: 42) and LCDR3 of QQSYSTPWT (SEQ ID NO: 43);

(c) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSEKYYVDSVKG (SEQ ID NO: 39) and HCDR3 of QLYFFDY (SEQ ID NO: 45); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQS (SEQ ID NO: 42) and LCDR3 of QQSYSTPWT (SEQ ID NO: 43);

(d) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSEKYYVDSVKG (SEQ ID NO: 39) and HCDR3 of QLYAFDY (SEQ ID NO: 46); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQS (SEQ ID NO: 42) and LCDR3 of QQSYSTPWT (SEQ ID NO: 43);

(e) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSETYYVDSVKG (SEQ ID NO: 48) and HCDR3 of QLYGFDY (SEQ ID NO: 40); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQS (SEQ ID NO: 42) and LCDR3 of QQSYSIPWT (SEQ ID NO: 47); or

(f) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGAEKYYVDSVKG (SEQ ID NO: 49) and HCDR3 of QLYGFDY (SEQ ID NO: 40); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQD (SEQ ID NO: 50) and LCDR3 of QQSYSTPWT (SEQ ID NO: 43);

~~(g) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSETYYVDSVKG (SEQ ID NO: 48), and HCDR3 of~~

~~QLYGFDY (SEQ ID NO: 40); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQS (SEQ ID NO: 42), and LCDR3 of QQSYSTPWT (SEQ ID NO: 47);~~

~~(h) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGAEKYYVDSVKG (SEQ ID NO: 49), and HCDR3 of QLYGFDY (SEQ ID NO: 40); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQD (SEQ ID NO: 50), and LCDR3 of QQSYSTPWT (SEQ ID NO: 43);~~

~~(i) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSNTYYVDSVKG (SEQ ID NO: 51), and HCDR3 of QLYGFDY (SEQ ID NO: 40); and the VL region amino acid sequence comprises LCDR1 of RASQSISTWLN (SEQ ID NO: 52), LCDR2 of AASSLAS (SEQ ID NO: 53), and LCDR3 of QQSYSTPWT (SEQ ID NO: 43);~~

~~(j) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSEKYYVDSVKG (SEQ ID NO: 39), and HCDR3 of QVYYFDY (SEQ ID NO: 44); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLHS (SEQ ID NO: 54), and LCDR3 of QQSYSTPWT (SEQ ID NO: 43); or~~

~~(k) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSEKYYVDSVKG (SEQ ID NO: 39), and HCDR3 of QVYYFDY (SEQ ID NO: 44); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQS (SEQ ID NO: 42), and LCDR3 of QQSYSTPWT (SEQ ID NO: 43).~~

2. The antibody or antigen-binding portion of claim 1, wherein

(a) the VH region amino acid sequence comprises SEQ ID NO:1 and the VL region amino acid sequence comprises SEQ ID NO:2;

(b) the VH region amino acid sequence comprises SEQ ID NO:3 and the VL region amino acid sequence comprises SEQ ID NO:4;

(c) the VH region amino acid sequence comprises SEQ ID NO:5 and the VL region amino acid sequence comprises SEQ ID NO:6;

(d) the VH region amino acid sequence comprises SEQ ID NO:7 and the VL region amino acid sequence comprises SEQ ID NO:8;

(e) the VH region amino acid sequence comprises SEQ ID NO:9 and the VL region amino acid sequence comprises SEQ ID NO:10; or

(f) the VH region amino acid sequence comprises SEQ ID NO:11 and the VL region amino acid sequence comprises SEQ ID NO:12.

3. The antibody or antigen-binding portion of any one of claims 1-2, wherein the antibody is humanized or chimeric.
4. The antibody or antigen-binding portion of any one of claims 1-3, wherein the VH region, the VL region, or both the VH and the VL region comprise one or more human framework region amino acid sequences.
5. The antibody or antigen-binding portion of any one of claims 1-4, wherein the VH region, the VL region, or both the VH and the VL region comprise a human variable region framework scaffold amino acid sequence into which the CDRs have been inserted.
6. The antibody or antigen-binding portion of claim 1, wherein the VH region comprises an IGHV3-7 human germline scaffold amino acid sequence into which the HCDR1, HCDR2 and HCDR3 amino acid sequences have been inserted.
7. The antibody or antigen-binding portion of any one of claims 1 and 6, wherein the VL region comprises an IGKV1-39 human germline scaffold amino acid sequence into which the LCDR1, LCDR2 and LCDR3 amino acid sequences have been inserted.
8. The antibody or antigen-binding portion of any one of claims 1-7, wherein the antibody comprises an immunoglobulin constant region.
9. The antibody or antigen-binding portion of claim 8, wherein the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA or IgY.
10. The antibody or antigen-binding portion of claim 9, wherein the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2.
11. The antibody or antigen-binding portion of claim 8, wherein the immunoglobulin constant region is immunologically inert.
12. The antibody or antigen-binding portion of claim 8, wherein the immunoglobulin constant region is a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and

G237A or a wild-type human IgG2 constant region, wherein numbering is according to the EU index as in Kabat.

13. The antibody or antigen-binding portion of claim 8, wherein the immunoglobulin constant region comprises any one of SEQ ID NOS:13-19.

14. The antibody or antigen-binding portion of any one of claims 1-13, wherein the antibody or antigen-binding portion is an Fab, an Fab', an F(ab')₂, an Fv, an scFv, a maxibody, a minibody, a diabody, a triabody, a tetrabody or a bis-scFv.

15. The antibody or antigen-binding portion of any one of claims 1-14, wherein the antibody is monoclonal.

16. The antibody or antigen-binding portion of any one of claims 1-15, wherein the antibody is a tetrameric antibody, a tetravalent antibody or a multispecific antibody.

17. The antibody or antigen-binding portion of any one of claims 1-16, wherein the antibody is a bispecific antibody that binds specifically to a first antigen and a second antigen, wherein the first antigen is PD1 and the second antigen is not PD1.

18. The antibody or antigen-binding portion of any one of claims 1-17, wherein the antibody or antigen-binding portion binds specifically to (a) human PD1 or (b) human PD1 and cynomolgus PD1.

19. The antibody or antigen-binding portion of any one of claims 1-18, wherein the antibody or antigen-binding portion is in an IgG1 format and wherein the antigen-binding portion has a melting temperature (T_m) from about 90°C to about 93°C.

~~20. The antibody or antigen-binding portion of any one of claims 1-19, wherein the antibody or antigen-binding portion undergoes reduced oxidation of exposed amino acid residues compared to an anti-PD1 antibody comprising the variable domain sequences of humanized antibody Mab005.~~

~~24~~20. An immunoconjugate comprising the antibody or antigen-binding portion of any one of claims ~~1-20~~1-19 linked to a therapeutic agent.

~~22~~21. The immunoconjugate of claim ~~24~~20, wherein the therapeutic agent is a cytotoxin, a radioisotope, a chemotherapeutic agent, an immunomodulatory agent, a cytostatic enzyme, a cytolytic enzyme, a therapeutic nucleic acid, an anti-angiogenic agent, an anti-proliferative agent, or a pro-apoptotic agent.

~~23~~22. A pharmaceutical composition comprising the antibody or antigen-binding portion of any one of claims ~~1-20~~1-19 or the immunoconjugate of claim ~~24~~20 or ~~22~~21, and a pharmaceutically acceptable carrier, diluent or excipient.

~~24~~23. A nucleic acid molecule encoding
~~—— (a) the VH region amino acid sequence;~~
~~—— (b) the VL region amino acid sequence; or~~
~~—— (c) both the VH region and the VL region amino acid sequences~~
of the antibody or antigen-binding portion of any one of claims ~~1-20~~1-19.

~~25~~24. An expression vector comprising the nucleic acid molecule of claim ~~24~~23.

~~26~~25. A recombinant host cell comprising the nucleic acid molecule of claim ~~24~~23 or the expression vector of claim ~~25~~24.

~~27~~26. A method of producing an anti-PD1 antibody or an antigen-binding portion thereof, the method comprising:

culturing a recombinant host cell comprising the expression vector of claim ~~25~~24 under conditions whereby the nucleic acid molecule is expressed, thereby producing the antibody or antigen-binding portion; and
isolating the antibody or antigen-binding portion from the host cell or culture.

~~28~~27. Use of a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims ~~1-20~~1-19, the immunoconjugate of claim ~~24~~20 or ~~22~~21 or the pharmaceutical composition of claim ~~23~~22 in the manufacture of a medicament for enhancing an immune response in a subject, wherein the medicament is to be administered to the subject.

~~29~~28. Use of a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims ~~1-20~~1-19, the immunoconjugate of claim ~~24~~20 or ~~22~~21 or the pharmaceutical composition of claim ~~23~~22 in the manufacture of a medicament for the

treatment or prevention of cancer; ~~or an infectious disease, or an immune disease~~ in a subject, wherein the medicament is to be administered to the subject.

~~3029~~. The use of claim ~~2928~~, wherein the cancer is pancreatic cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, or cancer of hematological tissues.

~~3430~~. The use of claim ~~2928~~, wherein the infectious disease is viral, bacterial, fungal, or parasitic.

~~3231~~. The use of claim ~~2928~~, wherein the infectious disease is human immunodeficiency virus (HIV) infection.

~~3332~~. The use of any one of claims ~~28-3227-31~~, wherein the administration of the antibody molecule, the antigen-binding portion, the immunoconjugate, or the pharmaceutical composition does not induce or induces minimal hemangioma in the subject.

~~3433~~. The antibody or antigen-binding portion of any one of claims ~~1-201-19~~, the immunoconjugate of claim ~~24-20~~ or ~~22-21~~ or the pharmaceutical composition of claim ~~23-22~~ for use in the treatment of cancer; ~~or an infectious disease, or an immune disease~~.

~~3534~~. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim ~~3433~~, wherein the cancer is pancreatic cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, or cancer of hematological tissues.

~~36~~35. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim ~~34~~33, wherein the infectious disease is viral, bacterial, fungal, or parasitic.

~~37~~36. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim ~~34~~33, wherein the infectious disease is human immunodeficiency virus (HIV) infection.

~~38~~37. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim ~~34~~33, wherein the use of the antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition in the treatment of cancer, or an infectious disease, ~~or an immune disease~~ does not induce or induces minimal hemangioma.

~~39~~38. The antibody or antigen-binding portion of any one of claims ~~1-20~~1-19, the immunoconjugate of claim ~~24~~20 or ~~22~~21 or the pharmaceutical composition of claim ~~23~~22, for use as a medicament.