Ala; (c) n = 3 and each X = Ala; (d) n = 2 and at least one X = Ala and wherein the remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid; (e) n = 3 and at least one X = Ala and wherein the remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid; (f) n = 3 and at least two X = Ala and wherein the remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid; (g) n = 1 and X = Gly; (h) n = 2 and each X = Gly; (i) n = 3 and each X = Gly; (j) n = 2 and at least one X = Gly wherein the remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid; (k) n = 3 and at least one X = Gly wherein the remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid; (l) n = 3 and at least two X = Gly wherein the remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid; (m) n = 2 and each X = Ala or Gly; (n) n = 3 and each X = Ala or Gly; (o) n = 3 and at least one X = Ala or Gly wherein remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid; or (p) n = 3 and at least two X = Ala or Gly wherein the remaining amino acid residue(s) X are independently chosen from any naturally occurring amino acid, *e.g.*, A, AA, AAA, G, GG, GGG, AG, GA, AAG, AGG, AGA, GGA, GAA or GAG. The present disclosure also provides a PD1 binder (*e.g.*, an ISVD such as a Nanobody) comprising one or mutations at position 11, 89, 110 and 112 and an amino acid sequence having at least 85% (*e.g.*, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, 99.9 or 100%) sequence identity with the amino acid sequence set forth in a member selected from the group consisting of SEQ ID NOs: 9-40 (in which any C-terminal extension that may be present as well as any CDRs are not taken into account for determining the degree of sequence identity).

In one aspect, there is provided a PD1 binder comprising an immunoglobulin single variable domain (ISVD) that binds to PD1, wherein the immunoglobulin single variable domain comprises the amino acid sequence:

DVQLVESGGG VVQPGGSLRL SCAASGSIAS IHAMGWFRQA PGKEREFVAV ITWSGGITYY
ADSVKGRFTI SRDNSKNTVY LQMNSLRPED TALYYCAGDK HQSSWYDYWG QGTLVTVSS

(SEQ ID NO: 57)~~,~~ or said sequence comprising a D1E mutation~~)~~;

EVQLVESGGGVVQPGGSLRLSCAASGSIASIHAMGWFRQAPGKEREFVAVITWSGGITYYADSVKGRFTISRDNSKNT
VYLQMNSLRPEDTALYYCAGDKHQSSWYDYWGQGTLVTVSS

(SEQ ID NO: 99)~~,~~ or said sequence comprising a E1D mutation~~)~~;

DVQLVESGGGVVQPGGSLRLSCAASGSIASIHAMGWFRQAPGKEREFVAVITVSGGITYYADSVKGRFTISRDNSKNT
VYLQMNSLRPEDTALYYCAGDKHQSSFYDYWGQGTLVTVSS

(SEQ ID NO: 103)~~,~~ or said sequence comprising a D1E and/or N73S mutation~~)~~;

DVQLVESGGGVVQPGGSLRLSCAASGSIASIHAMGWFRQAPGKEREFVAVITVSGGITYYADSVKGRFTISRDQSKNT
VYLQMNSLRPEDTALYYCAGDKHQSSFYDYWGQGTLVTVSS

(SEQ ID NO: 104)~~,~~ or said sequence comprising a D1E mutation~~)~~; or

DVQLVESGGGVVQPGGSLRLSCAASGSIASIHAMGWFRQAPGKEREFVAVITVSGGITYYADSVKGRFTISRDPSKNT
VYLQMNSLRPEDTALYYCAGDKHQSSFYDYWGQGTLVTVSS

(SEQ ID NO: 105)~~,~~ or said sequence comprising a D1E mutation~~)~~, or

DVQLVESGGGVVQPGGSLRLSCAASGSIASIHAMGWFRQAPGKEREFVAVITVSGGITYYADSVKGRFTISRDQSKNT
VYLQMNSLRPEDTALYYCAGDKHQSSFYDYWGQGTLVTVSS (amino acids 1-119 of SEQ ID NO: 117)~~,~~ or said sequence comprising a D1E mutation~~)~~; or

DVQLVESGGGVVQPGGSLRLSCAASGSIASIHAMGWFRQAPGKEREFVAVITVSGGITYYADSVKGRFTISRDSSKNT
VYLQMNSLRPEDTALYYCAGDKHQSSFYDYWGQGTLVTVSS (amino acids 1-119 of SEQ ID NO: 121)~~,~~ or said sequence comprising a D1E mutation~~)~~;

and, optionally, comprising a half-life extender and/or a C-terminal extender.

The present disclosure also provides a multispecific immunoglobulin comprising a PD1 binder (*e.g.*, an ISVD such as a Nanobody) that binds to PD1 linked to one or more molecules that bind to an epitope that is not the epitope to which the PD1 binder binds (*e.g.*, PD1, CTLA4, LAG3, BTLA and/or CD27), *e.g.*, comprising a PD1 binding moiety and a CTLA4 binding moiety; a PD1 binding moiety and a BTLA binding moiety; a PD1 binding moiety and a LAG3 binding moiety; or a PD1 binding moiety, a LAG3 binding moiety and a BTLA binding moiety, optionally linked via one or more linkers, *e.g.*, peptide linkers. In one embodiment, the multispecific immunoglobulin comprises a first PD1 Nanobody linked to one or more molecules selected from the group consisting of an CTLA4 Nanobody, an LAG3 Nanobody, an BTLA Nanobody, an

**We claim**:

1. A PD1 binder comprising an immunoglobulin single variable domain (ISVD) that binds to PD1, wherein the immunoglobulin single variable domain comprises the amino acid sequence:

DVQLVESGGG VVQPGGSLRL SCAASGSIAS IHAMGWFRQA PGKEREFVAV ITWSGGITYY ADSVKGRFTI SRDNSKNTVY LQMNSLRPED TALYYCAGDK HQSSWYDYWG QGTLVTVSS

(SEQ ID NO: 57), or said sequence comprising a D1E mutation);

EVQLVESGGGVVQPGGSLRLSCAASGSIASIHAMGWFRQAPGKEREFVAVITWSGGITYYADSVKGRFTISRDNSKNT VYLQMNSLRPEDTALYYCAGDKHQSSWYDYWGQGTLVTVSS

(SEQ ID NO: 99), or said sequence comprising a E1D mutation);

DVQLVESGGGVVQPGGSLRLSCAASGSIASIHAMGWFRQAPGKEREFVAVITVSGGITYYADSVKGRFTISRDNSKNT VYLQMNSLRPEDTALYYCAGDKHQSSFYDYWGQGTLVTVSS

(SEQ ID NO: 103), or said sequence comprising a D1E and/or N73S mutation);

DVQLVESGGGVVQPGGSLRLSCAASGSIASIHAMGWFRQAPGKEREFVAVITVSGGITYYADSVKGRFTISRDQSKNT VYLQMNSLRPEDTALYYCAGDKHQSSFYDYWGQGTLVTVSS

(SEQ ID NO: 104), or said sequence comprising a D1E mutation); or

DVQLVESGGGVVQPGGSLRLSCAASGSIASIHAMGWFRQAPGKEREFVAVITVSGGITYYADSVKGRFTISRDPSKNT VYLQMNSLRPEDTALYYCAGDKHQSSFYDYWGQGTLVTVSS

(SEQ ID NO: 105), or said sequence comprising a D1E mutation), or

DVQLVESGGGVVQPGGSLRLSCAASGSIASIHAMGWFRQAPGKEREFVAVITVSGGITYYADSVKGRFTISRDQSKNT VYLQMNSLRPEDTALYYCAGDKHQSSFYDYWGQGTLVTVSS (amino acids 1-119 of SEQ ID NO: 117), or said sequence comprising a D1E mutation); or

DVQLVESGGGVVQPGGSLRLSCAASGSIASIHAMGWFRQAPGKEREFVAVITVSGGITYYADSVKGRFTISRDSSKNT VYLQMNSLRPEDTALYYCAGDKHQSSFYDYWGQGTLVTVSS (amino acids 1-119 of SEQ ID NO: 121), or said sequence comprising a D1E mutation);

and, optionally, comprising a half-life extender and/or a C-terminal extender.

2. The PD1 binder of calim 1, wherein the PD1 binder is linked at the C-terminus to a half-life extender comprising the amino acid sequence of SEQ ID NO: 59.

3. The PD1 binder of claim 1 or 2 further comprising a C-terminal extender wherein the C-terminal extender is an alanine.

4. An injection device or vessel that comprises the binder of any one of claims 1 to 3.

5. A polynucleotide encoding the binder of any one of claims 1 to 3.

6. A vector comprising the polynucleotide of claim 5.

7. A host cell comprising the polynucleotide of claim 5 or the vector of claim 6.

8. A method for making a PD1 binder of any one of claims 1 to 3 comprising introducing a polynucleotide encoding the binder into a host cell and culturing the host cell in a medium under conditions favorable to expression of said binder from said polynucleotide and, optionally, purifying the binder from said host cell and/or said medium.

9. A PD1 binder produced by the method of claim 8.

10. A method for preventing PD1 from binding to PD-L1 and/or PD-L2 in vitro comprising contacting the PD1 with said binder of any one of claims 1 to 3 optionally in association with a further therapeutic agent.

11. A PD1 binder of any one of claims 1 to 3 for use in enhancing an immune response in a subject, optionally in association with a further therapeutic agent.

12. Use of a PD1 binder of any one of claims 1 to 3 in the manufacture of a medicament for the treatment of cancer or an infectious disease.

13. The use of claim 12 wherein the cancer is metastatic cancer, a solid tumor, a hematologic cancer, leukemia, lymphoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma, kidney cancer, leukemia, renal transitional cell cancer, bladder cancer, Wilm’s cancer, ovarian cancer, pancreatic cancer, breast cancer, prostate cancer, bone cancer, lung cancer, non-small cell lung cancer, gastric cancer, colorectal cancer, cervical cancer, synovial sarcoma, head and neck cancer, squamous cell carcinoma, multiple myeloma, renal cell cancer, retinoblastoma, hepatoblastoma, hepatocellular carcinoma, melanoma, rhabdoid tumor of the kidney, Ewing's sarcoma, chondrosarcoma, brain cancer, glioblastoma, meningioma, pituitary adenoma, vestibular schwannoma, a primitive neuroectodermal tumor, medulloblastoma, astrocytoma, anaplastic astrocytoma, oligodendroglioma, ependymoma, choroid plexus papilloma, polycythemia vera,

thrombocythemia, idiopathic myelfibrosis, soft tissue sarcoma, thyroid cancer, endometrial cancer, carcinoid cancer or liver cancer, breast cancer or gastric cancer.

14. The use of claim 12 wherein the infectious disease is a bacterial infection, a viral infection or a fungal infection.

15. The use of any one of claims 12-14 wherein the medicament is to be administered in association with other, further therapeutic agents and/or therapeutic procedures.