

immunotherapeutic agents with increased potency and efficacy for use in the treatment of cancer.

In one aspect, the present disclosure provides a multispecific antigen-binding construct comprising at least two antigen-binding arms, wherein: a first arm binds PD-1 and comprises a heavy chain variable region and a light chain variable region, the heavy chain variable region of the first arm comprising a CDRH1 of SEQ ID NO: 77, a CDRH2 of SEQ ID NO: 71, and a CDRH3 of SEQ ID NO: 75, and a second arm binds a PD-1 ligand and comprises a heavy chain variable region and a light chain variable region, the heavy chain variable region of the second arm comprising a CDRH1 of SEQ ID NO: 1, a CDRH2 of SEQ ID NO: 7, and a CDRH3 of SEQ ID NO: 8; wherein the light chain variable region of the first arm and the light chain variable region of the second arm each comprise a CDRL1 of SEQ ID NO: 9, a CDRL2 of SEQ ID NO: 5, and a CDRL3 of SEQ ID NO: 10; and wherein the multispecific antigen-binding construct blocks the interaction of PD-1 and the PD-1 ligand.

In some embodimentexamples, any of the multispecific antigen-binding constructs disclosed herein binds to at least two different receptors or epitopes (*e.g.*, PD-1 and PD-L1), wherein the two different receptors or epitopes bound by the multispecific antigen-binding construct are expressed on the surface of the same cell. For example, in some

embodimentexamples, the multispecific antigen-binding construct simultaneously binds to PD-1 and PD-L1, wherein the PD-1 and PD-L1 are expressed on the surface of the same cell.

In some embodimentexamples, any of the multispecific antigen-binding constructs disclosed herein binds to at least two different receptors or epitopes (*e.g.*, PD-1 and PD-L1), wherein the two different receptors or epitopes bound by the multispecific antigen-binding construct are expressed on the surface of two different cells. For example, in some

embodimentexamples, the multispecific antigen-binding construct simultaneously binds to PD-1 expressed on the surface of a first cell and to a PD-1 ligand, *e.g.*, PD-L1 or PD-L2, expressed on the surface of a second cell.

In some embodimentexamples, the disclosure provides for a multispecific antigen-binding construct comprising at least two antigen-binding arms, wherein a first arm binds PD-1 expressed by an immune cell, and a second arm binds a PD-1 ligand which is expressed by a second cell, wherein the multispecific antigen-binding construct blocks the interaction of PD-1 and PD-1 ligand. In some embodimentexamples, the PD-1 ligand is PD-L2. In some embodimentexamples, the PD-1 ligand is PD-L1. In some embodimentexamples, the

immune cell is a T cell. In some embodimentexamples, the T cell is a CD8+ T cell. In some embodimentexamples, the immune cell is a natural killer (NK) cell. In some embodimentexamples, the immune cell is a macrophage. In some embodimentexamples, the second cell is a second immune cell. In some embodimentexamples, the second immune cell is any one or more of a T cell, a B cell, a macrophage, a myeloid-derived suppressor cell, a dendritic cell, or a mesenchymal stromal cell. In some embodimentexamples, the second immune cell is a regulatory T cell. In some embodimentexamples, the second cell is a tumor cell. In some embodimentexamples, the tumor cell is selected from the group consisting of a hematological cancer, a lymphoma, a myeloma, a leukemia, a neurological cancer, melanoma, breast cancer, a prostate cancer, a colorectal cancer, lung cancer, head and neck cancer, a gastrointestinal cancer, liver cancer, pancreatic cancer, a genitourinary cancer, a bone cancer, renal cancer, and a vascular cancer. In some embodimentexamples, both arms have a K_D of at least 1×10^{-7} M, at least 1×10^{-8} M, at least 1×10^{-9} M, or at least 1×10^{-10} M. In some embodimentexamples, the binding of one arm to its target does not block the binding of the other arm to its target. In some embodimentexamples, the first arm and second arm bind to their respective

targets and both arms remain bound concurrently. In some [embodimentexamples](#), binding of the first arm and the second arm to their respective targets can bridge the immune cell and the second cell together. In some [embodimentexamples](#), the bridging of the immune cell and the second cell is determined by flow cytometry. In some [embodimentexamples](#), the first arm is an antagonist of PD-1.

In some [embodimentexamples](#) of the multispecific antigen-binding constructs, the first arm binds to PD-1 and comprises: (a) a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 70 (FTFX₁X₂YAX₃X₄, wherein X₁=S, R, G, or N; X₂=D, S, N, A, R, or G; X₃=M or L; X₄=S, L, or N); (ii) a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYTYA); and (iii) a CDRH3 comprising SEQ ID NO: 72 (ARGLDFIVGX₅TGNDY, wherein X₅=A, Y, or R); and (b) a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

In some [embodimentexamples](#), the CDRH1 of the first arm comprises SEQ ID NO: 73 (FTFSDYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYTYA) and CDRH3 of the first arm comprises SEQ ID NO: 74 (ARGLDFIVGATGNDY). In some [embodimentexamples](#), the CDRH1 of the first arm comprises SEQ ID NO: 73 (FTFSDYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYTYA) and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY). In some [embodimentexamples](#), the CDRH1 of the first arm comprises SEQ ID NO: 76 (FTFSSYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYTYA) and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY). In some [embodimentexamples](#), the CDRH1 of the first arm comprises SEQ ID NO: 77 (FTFSSYAML), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYTYA) and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY). In some [embodimentexamples](#), the CDRH1 of the first arm comprises SEQ ID NO: 78 (FTFSNYALS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYTYA) and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY). In some [embodimentexamples](#), the CDRH1 of the first arm comprises SEQ ID NO: 79 (FTFSAYAMN), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYTYA) and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY). In some [embodimentexamples](#), the CDRH1 of the first arm comprises SEQ ID NO: 80 (FTFRSYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYTYA) and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY). In some [embodimentexamples](#), the CDRH1 of the first arm comprises

SEQ ID NO: 81 (FTFGRYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA) and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY). In some [embodimentexamples](#), the CDRH1 of the first arm comprises SEQ ID NO: 82 (FTFNSYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA) and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY). In some [embodimentexamples](#), the CDRH1 of the first arm comprises SEQ ID NO: 83 (FTFSNYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA) and CDRH3 of the first arm comprises SEQ ID NO: 74 (ARGLDFIVGATGNDY). In some [embodimentexamples](#), the CDRH1 of the first arm comprises SEQ ID NO: 84 (FTFSGYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA) and CDRH3 of the first arm comprises SEQ ID NO: 85 (ARGLDFIVGRTGNDY). In some [embodimentexamples](#), the CDRH1 of the first arm comprises SEQ ID NO: 86 (FTFSSYAMN), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA) and CDRH3 of the first arm comprises SEQ ID NO: 85 (ARGLDFIVGRTGNDY). In some [embodimentexamples](#), the CDRH1 of the first arm comprises SEQ ID NO: 80 (FTFRSYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA) and CDRH3 of the first arm comprises SEQ ID NO: 85 (ARGLDFIVGRTGNDY).

In some [embodimentexamples](#), the CDRL1 of the first arm comprises SEQ ID NO: 9 (RASQSISSYLN), CDRL2 of the first arm comprises SEQ ID NO: 5 (AASSLQS) and CDRL3 of the first arm comprises SEQ ID NO: 10 (QQSYSTPLT).

In some [embodimentexamples](#), the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 87. In some [embodimentexamples](#), the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 88. In some [embodimentexamples](#), the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 89. In some [embodimentexamples](#), the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 90. In some [embodimentexamples](#), the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 91. In some [embodimentexamples](#), the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 92. In some [embodimentexamples](#), the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 93. In some [embodimentexamples](#), the heavy chain variable region of the first arm comprises an amino

acid sequence that is at least 90% identical to SEQ ID NO: 94. In some embodimentexamples, the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 95. In some embodimentexamples, the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 96. In some embodimentexamples, the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 97. In some embodimentexamples, the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 98. In some embodimentexamples, the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 99. In some embodimentexamples, the light chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 59.

In some embodimentexamples, the second arm is an antagonist of the PD-1 ligand. In some embodimentexamples, the second arm is an antagonist of PD-L2. In some embodimentexamples, the second arm is an antagonist of PD-L1. In some embodimentexamples, the second arm binds to PD-L1 and comprises: a. a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN); (ii) a CDRH2 comprising SEQ ID NO: 2 (GGIIPX₁X₂GX₃ATYA, wherein X₁ is V or I; X₂ is F, L, or V; and X₃ is T or A); and (iii) a CDRH3 comprising SEQ ID NO: 3 (ARLKX₁ELKDAFDI, wherein X₁ is G, F, or N); and b. a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 4 (RASQX₁ISSYLN, wherein X₁ is S, W, or Q); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 6 (X₁QSYSTPLT, wherein X₁ is Q or F).

In some embodimentexamples, the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 7 (GGIIPILGAATYA) and CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI). In some embodimentexamples, the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 7 (GGIIPILGAATYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

In some embodimentexamples, the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm

comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT). In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA) and CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI). In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second arm comprises SEQ ID NO: 12 (RASQWISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT). In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second arm comprises SEQ ID NO: 13 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT). In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 15 (GGIPIFGIANYA) and CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI). In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 15 (GGIPIFGIANYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 16 (GGIIPNFGTATYA) and CDRH3 of the second arm comprises SEQ ID NO: 17 (ARLKGELKGAGDI). In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN),

CDRH2 of the second arm comprises SEQ ID NO: 16 (GGIIPNFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 17 (ARLKGELKGAGDI); CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10

5 (QQSYSTPLT).

In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), and CDRH3 of the second arm comprises SEQ ID NO: 18

(ARLKFELKDAFDI). In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 18 (ARLKFELKDAFDI), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

15 In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), and CDRH3 of the second arm comprises SEQ ID NO: 19 (ARLKGELKDAFDE). In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 19 (ARLKGELKDAFDE), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

25 In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), and CDRH3 of the second arm comprises SEQ ID NO: 20 (ARLKNELKDAFDI). In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 20 (ARLKNELKDAFDI), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

In some [embodimentexamples](#), the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 21

(GGVIPFLGTANYA), and CDRH3 of the second arm comprises SEQ ID NO: 22 (ARLKGILKDALDI). In some embodimentexamples, the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 21 (GGVIPFLGTANYA), CDRH3 of the second arm comprises SEQ ID NO: 22 (ARLKGILKDALDI), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

In some embodimentexamples, the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 29 (GRIIPFGTADYA), and CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI). In some embodimentexamples, the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 29 (GRIIPFGTADYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

In some embodimentexamples, the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 31 (GGIIPILGTATYA), and CDRH3 of the second arm comprises SEQ ID NO: 32 (ARRKGELKDAFDI). In some embodimentexamples, the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 31 (GGIIPILGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 32 (ARRKGELKDAFDI), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

In some embodimentexamples, the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 33 (GGIPIVATANYA), and CDRH3 of the second arm comprises SEQ ID NO: 32 (ARRKGELKDAFDI). In some embodimentexamples, the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 33 (GGIPIVATANYA), CDRH3 of the second arm comprises SEQ ID NO: 32 (ARRKGELKDAFDI), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

In some embodimentexamples, the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 34 (GGIPIFGKATYA), and CDRH3 of the second arm comprises SEQ ID NO: 32 (ARRKGELKDAFDI). In some embodimentexamples, the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 34 (GGIPIFGKATYA), CDRH3 of the second arm comprises SEQ ID NO: 32 (ARRKGELKDAFDI), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

In some embodimentexamples, the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 38 (FQSYSTPLT).

In some embodimentexamples, the CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 39 (QQSYSTILT).

In some embodimentexamples, the second arm comprises: a. a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 14 (GTFSSYAFS), (ii) a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA) and (iii) a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI); and b. a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

In some embodimentexamples, the second arm comprises a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 23 (GTFSSYAIS), (ii) a CDRH2 comprising SEQ ID NO: 24 (GGIPIVGIANYA), and (iii) a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI). In some embodimentexamples, the second arm comprises a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

In some embodimentexamples, the second arm comprises a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), (ii) a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), and (iii) a CDRH3 comprising SEQ ID NO: 25 (ARLKGEFKDAFDI). In some embodimentexamples, the second arm comprises a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

In some embodimentexamples, the second arm comprises a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), (ii) a CDRH2 comprising SEQ ID NO: 26 (GRIIPLFGTAHYA), and (iii) a CDRH3 comprising SEQ ID NO: 8 (ARLKGEFKDAFDI). In some embodimentexamples, the second arm comprises a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

In some embodimentexamples, the second arm comprises a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), (ii) a CDRH2 comprising SEQ ID NO: 27 (GRINPILGTANYA), and (iii) a CDRH3 comprising SEQ ID NO: 28 (ARLKGEFKDAFSI). In some embodimentexamples, the second arm comprises a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

In some embodimentexamples, the second arm comprises a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), (ii) a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), and (iii) a CDRH3 comprising SEQ ID NO: 30 (ARLKGEFKCAFDI). In some embodimentexamples, the second arm comprises a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

In some embodimentexamples, the second arm comprises a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 122 (GTKSSY AIS), (ii) CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), and (iii) a CDRH3 comprising SEQ ID NO: 30 (ARLKGEFKCAFDI). In some embodimentexamples, the second arm further comprises a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9

(RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

In some embodimentexamples, the second arm comprises a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 36 (GPFRSHAVS), (ii) a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), and (iii) a CDRH3 comprising SEQ ID NO: 37 (ARLKSELKDAFDI). In some embodimentexamples, the second arm comprises a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

In some embodimentexamples, the second arm that binds PD-L1 comprises a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 35, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, or 58 and a light chain variable region comprising an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 59, 60, 61, 62, or 63.

In some embodimentexamples, the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 35 (QVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAINWVRQAPGQGLEWMGGIIPVFGTATYAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARLKGELKDAFDIWGQGTMTV VSS). In some embodimentexamples, the heavy chain variable region of the second arm

comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 40 (QVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAFSWVRQAPGQGLEWMGGIIPVFGTATYAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARLKGELKDAFDIWGQGTTLTV VSS). In some embodimentexamples, the heavy chain variable region of the second arm

comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 41 (QVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAINWVRQAPGQGLEWMGGIIPFGIAN YAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARLKGELKDAFDIWGQGTTLTVT SS). In some embodimentexamples, the heavy chain variable region of the second arm comprises

an amino acid sequence that is at least 90% identical to SEQ ID NO: 42 (QVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAINWVRQAPGQGLEWMGGIIPNFGTATYAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARLKGELKGAGDIWGQGTTLTV VSS). In some embodimentexamples, the heavy chain variable region of the second arm

comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 43 (QVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAINWVRQAPGQGLEWMGGIIPVFGTATYAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARLKFELKDAFDIWGQG

TLVTVSS). In some [embodimentexamples](#), the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 44

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAINWVRQAPGGGLEWMGGIIPVFGTA
TYAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCARLKGELKDAFDEWGQGT

5 VSS). In some [embodimentexamples](#), the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 45

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAINWVRQAPGGGLEWMGGIIPVFGTA
TYAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCARLKGELKDAFDIWGQGT

10 AST). In some [embodimentexamples](#), the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 46

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAINWVRQAPGGGLEWMGGIIPVFGTA
TYAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCARLKNELKDAFDIWGQGT

VSS). In some [embodimentexamples](#), the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 47

15 (QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAINWVRQAPGGGLEWMGGVIPFLGTA
NYAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCARLKGILKDALDIWGQGT

VSS). In some [embodimentexamples](#), the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 48

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQDLEWMGGIIPVIGIAN
20 YAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCARLKGELKDAFDIWGQGT

SS). In some [embodimentexamples](#), the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 49

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGGGLEWMGGIIPVFGTA
TYAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCARLKGELKDAFDIWGQGT

25 VSS). In some [embodimentexamples](#), the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 50

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGGGLEWMGRIPFLGTA
HYAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCARLKGELKDAFDIWGQGT

30 VSS). In some [embodimentexamples](#), the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 51

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGGGLEWMGRINPILGTA
NYAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCARLKGELKDAFSIWGQGT

VSS). In some [embodimentexamples](#), the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 52

(QVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAINWVRQAPGQGLEWMGRIIPFG
TADYAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARLKGELKDAFDIWGQ
GTLVTVSS). In some [embodimentexamples](#), the heavy chain variable region of the second
arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 53

(QVQLVQSGAEVKKPGSSVKVSCASGGKFSSYAIWVRQAPGQGLEWMGGIIPVFG
TATYAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARLKGELKCAFDIWGQ
GTLVTVSS). In some [embodimentexamples](#), the heavy chain variable region of the second
arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 54

(QVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAINWVRQAPGQGLEWMGGIIPILG
TATYAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARRKGELKDAFDIWGQ
GTLVTVSS). In some [embodimentexamples](#), the heavy chain variable region of the second
arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 55

(QVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAINWVRQAPGQGLEWMGGIIPILG
AATYAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARLKGELKDAFDIWGQ
GTLVTVSS). In some [embodimentexamples](#), the heavy chain variable region of the second
arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 56

(QVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAINWVRQAPGQGLEWMGGIIPIVA
TANYAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARRKGELKDAFDIWGQ
GTLVTVSS). In some [embodimentexamples](#), the heavy chain variable region of the second
arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 57

(QVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAINWVRQAPGQGLEWMGGIIPFG
KATYAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARRKGELKDAFDIWGQ
GTLVTVSS). In some [embodimentexamples](#), the heavy chain variable region of the second
arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 58

(QVQLVQSGAEVKKPGSSVKVSCASGGPFRSHAVSWVRQAPGQGLEWMGGIIPVF
GTATYAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARLKSELKDAFDIWGQ
GTLVTVSS). In some [embodimentexamples](#), the light chain variable region of the second
arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 59

(DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPLTFGGGTKVEIK). In some
[embodimentexamples](#), the light chain variable region of the second arm comprises an amino
acid sequence that is at least 90% identical to SEQ ID NO: 60

(DIQMTQSPSSLSASVGDRVTITCRASQWISSYLNWYQQKPGKAPKLLIYAASSLQSG
VPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPLTFGGGTKVEIK). In some

embodimentexamples, the light chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 61

(DIQMTQSPSSLSASVGDRVTITCRASQQISSYLNWYQQKPGKAPKLLIYAASSLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK). In some

embodimentexamples, the light chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 62

(DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCFQSYSTPLTFGGGTKVEIK). In some

embodimentexamples, the light chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 63

(DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPS
RFGSGSGTDFTLTISSLQPEDFATYYCQQSYSTILTFGGGTKVEIK).

In some embodimentexamples of any of the aspectexamples described herein, the construct is a bispecific antibody. In some embodimentexamples, the bispecific antibody is an antagonist of both PD-1 and PD-1 ligand. In some embodimentexamples, the construct comprises a common light chain. In some embodimentexamples, one or both of the arms is an aptamer. In some embodimentexamples, one or both of the arms is a protein other than an antibody. In some embodimentexamples, the construct comprises at least two bispecific antibodies. In some embodimentexamples, one of the at least two bispecific antibodies is monovalent for PD-1. In some embodimentexamples, one of the at least two bispecific antibodies is monovalent for PD-1 ligand. In some embodimentexamples, at least one of the arms is a bivalent antibody specific for PD-1. In some embodimentexamples, at least one of the arms is a bivalent antibody specific for PD-L1. In some embodimentexamples, at least one of the arms is a bivalent antibody specific for PD-1, and at least one of the arms is a bivalent antibody specific for PD-L1. In some embodimentexamples, at least one of the arms is bivalent for PD-1. In some embodimentexamples, at least one of the arms is bivalent for PD-L1. In some embodimentexamples, at least one of the arms is bivalent for PD-1, and at least one of the arms is bivalent for PD-L1. In some embodimentexamples, the bispecific antibody binds two different epitopes on PD-1. In some embodimentexamples, the bispecific antibody binds two different epitopes on the PD-1 ligand.

In some embodimentexamples, any of the multispecific antigen-binding constructs disclosed herein comprises at least two monospecific antibodies. In some embodimentexamples, at least one of the monospecific antibodies is an anti-PD-1 antibody. In some embodimentexamples, the anti-PD-1 antibody is a bivalent anti-PD-1 antibody. In some embodimentexamples, at least one of the monospecific antibodies is an anti-PD-L1 antibody. In some embodimentexamples, the anti-PD-1

antibody is a bivalent anti-PD-L1 antibody. In some [embodimentexamples](#), the construct comprises a bivalent anti-PD-1 antibody and a bivalent anti-PD-L1 antibody. In some [embodimentexamples](#), the construct is a fusion construct in which a polypeptide comprising the variable heavy chain of the anti-PD-1 antibody is fused to a polypeptide comprising the variable heavy chain of the anti-PD-L1 antibody. In some [embodimentexamples](#), the polypeptide comprising the variable heavy chain of the anti-PD-1 antibody is fused to the polypeptide comprising the variable heavy chain of the anti-PD-L1 antibody by means of a linker. In some [embodimentexamples](#), the fusion construct comprises a common light chain. In some [embodimentexamples](#), the N-terminal variable heavy chain of the fusion construct binds to PD-1 in the presence of the common light chain, and the C-terminal variable heavy chain of the fusion construct binds to PD-L1 in the presence of the common light chain. In some [embodimentexamples](#), the N-terminal variable heavy chain of the fusion construct binds to PD-L1 in the presence of the common light chain, and the C-terminal variable heavy chain of the fusion construct binds to PD-1 in the presence of the common light chain.

In some [aspectexamples](#) and [embodimentexamples](#), the disclosure provides for a multispecific antigen-binding construct comprising at least two units of antigen-binding, wherein a first unit of antigen-binding binds PD-1, and a second unit of antigen-binding binds a PD-1 ligand. In some [embodimentexamples](#), the first unit of antigen-binding binds PD-1 expressed by an immune cell. In some [embodimentexamples](#), the second unit of antigen-binding binds PD-1 expressed by a second cell. In some [embodimentexamples](#), the multispecific antigen-binding construct blocks the interaction of PD-1 and a PD-1 ligand, such as PD-L1 or PD-L2. In some [embodimentexamples](#), the multispecific antigen-binding construct blocks the interaction of PD-1 and a PD-1 ligand, such as PD-L1 or PD-L2. In some [embodimentexamples](#), the multispecific antigen-binding construct comprises at least two units of antigen-binding that bind PD-1. In some [embodimentexamples](#), the multispecific antigen-binding construct comprises two units of antigen-binding that bind PD-1. In some [embodimentexamples](#), the multispecific antigen-binding construct comprises at least two units of antigen-binding that bind a PD-1 ligand, such as PD-L1 or PD-L2. In some [embodimentexamples](#), the multispecific antigen-binding construct comprises two units of antigen-binding that bind a PD-1 ligand, such as PD-L1 or PD-L2. In some [embodimentexamples](#), the multispecific antigen-binding construct comprises at least four units of antigen-binding, wherein two units of antigen-binding bind PD-1 and two units of antigen-binding bind a PD-1 ligand, such as PD-L1 or PD-L2. In some [embodimentexamples](#), the multispecific antigen-binding construct comprises four units of antigen-binding, wherein two units of antigen-binding bind PD-1 and two units of antigen-binding bind a PD-1 ligand, such as PD-L1 or PD-L2. In some

embodimentexamples, each unit of antigen-binding is capable of binding independently to its cognate antigen, *i.e.*, PD-1 or a PD-1 ligand, such as PD-L1 or PD-L2. In some embodimentexample, the multispecific antigen-binding construct promotes loss of PD-1 expression from a cell. In some embodimentexamples, the loss of PD-1 expression is due to PD-1 shedding. In some embodimentexamples, the multispecific antigen-binding construct blocks interaction of PD-1 and the PD-1 ligand, such as PD-L1 or PD-L2. In some embodimentexamples, the multispecific antigen-binding construct comprises a common light chain. For example, at least two units of antigen-binding comprise a common light chain.

In some embodimentexamples, the first unit of antigen-binding binds PD-1 and comprises:

(a) a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 70 (FTFX₁X₂YAX₃X₄, wherein X₁=S, R, G, or N; X₂=D, S, N, A, R, or G; X₃=M or L; X₄=S, L, or N); (ii) a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYTYA); and (iii) a CDRH3 comprising SEQ ID NO: 72 (ARGLDFIVGX₅TGNDY, wherein X₅=A, Y, or R); and

(b) a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

In some such embodimentexamples, the first unit of antigen-binding binds PD-1 and comprises:

(a) a CDRH1 comprising SEQ ID NO: 73 (FTFSDYAMS), a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYTYA), and a CDRH3 comprising SEQ ID NO: 74 (ARGLDFIVGATGNDY);

(b) a CDRH1 comprising SEQ ID NO: 73 (FTFSDYAMS), a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYTYA), and a CDRH3 comprising SEQ ID NO: 75 (ARGLDFIVGYTGNDY);

(c) a CDRH1 comprising SEQ ID NO: 76 (FTFSSYAMS), a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYTYA), and a CDRH3 comprising SEQ ID NO: 75 (ARGLDFIVGYTGNDY);

(d) a CDRH1 comprising SEQ ID NO: 77 (FTFSSYAML), a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYTYA), and a CDRH3 comprising SEQ ID NO: 75 (ARGLDFIVGYTGNDY);

(e) a CDRH1 comprising SEQ ID NO: 78 (FTFSNYALS), a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYTYA), and a CDRH3 comprising SEQ ID NO: 75 (ARGLDFIVGYTGNDY);

- (f) a CDRH1 comprising SEQ ID NO: 79 (FTFSAYAMN), a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYYA), and a CDRH3 comprising SEQ ID NO: 75 (ARGLDFIVGYTGNDY);
- (g) a CDRH1 comprising SEQ ID NO: 80 (FTFRSYAMS), a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYYA), and a CDRH3 comprising SEQ ID NO: 75 (ARGLDFIVGYTGNDY);
- (h) a CDRH1 comprising SEQ ID NO: 81 (FTFGRYAMS), a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYYA), and a CDRH3 comprising SEQ ID NO: 75 (ARGLDFIVGYTGNDY);
- (i) a CDRH1 comprising SEQ ID NO: 82 (FTFNSYAMS), a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYYA), and a CDRH3 comprising SEQ ID NO: 75 (ARGLDFIVGYTGNDY);
- (j) a CDRH1 comprising SEQ ID NO: 83 (FTFSNYAMS), a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYYA), and a CDRH3 comprising SEQ ID NO: 74 (ARGLDFIVGATGNDY);
- (k) a CDRH1 comprising SEQ ID NO: 84 (FTFSGYAMS), a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYYA), and a CDRH3 comprising SEQ ID NO: 85 (ARGLDFIVGRTGNDY);
- (l) a CDRH1 comprising SEQ ID NO: 86 (FTFSSYAMN), a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYYA) and a CDRH3 comprising SEQ ID NO: 85 (ARGLDFIVGRTGNDY); or
- (m) a CDRH1 comprising SEQ ID NO: 80 (FTFRSYAMS), a comprising SEQ ID NO: 71 (SAISNSGTYTYYA), and a CDRH3 comprising SEQ ID NO: 85 (ARGLDFIVGRTGNDY).

In some embodiment examples, the first unit of antigen-binding binds PD-1 and comprises:

- (a) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 87;
- (b) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 88;
- (c) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 89;
- (d) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 90;

- (e) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 91;
- (f) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 92;
- 5 (g) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 93;
- (h) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 94;
- 10 (i) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 95;
- (j) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 96;
- (k) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 97;
- 15 (l) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 98; or
- (m) a heavy chain variable region comprising amino acid sequence that is at least 90% identical to SEQ ID NO: 99.

20 In some embodimentexamples, the first unit of antigen-binding binds PD-1 and comprises a light chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 59.

In some embodimentexamples, the second unit of antigen-binding binds PD-L2. In some embodimentexamples, the second unit of antigen-binding binds PD-L1. In some embodimentexamples, the second unit of antigen-binding binds PD-L1 and comprises:

- 25 a. a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN); (ii) a CDRH2 comprising SEQ ID NO: 2 (GGIIPX₁X₂GX₃ATYA, wherein X₁ is V or I; X₂ is F, L, or V; and X₃ is T or A); and (iii) a CDRH3 comprising SEQ ID NO: 3 (ARLKX₁ELKDAFDI, wherein X₁ is G, F, or N); and
- b. a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 4 (RASQX₁ISSYLN, wherein X₁ is S, W, or Q); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 6 (X₁QSYSTPLT, wherein X₁ is Q or F).
- 30

In some such embodimentexamples, the second unit of antigen-binding binds PD-L1 and comprises:

- (a) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 7 (GGIIPILGAATYA), and a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI);
- 5 (b) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 7 (GGIIPILGAATYA), a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI); a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- 10 (c) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI); a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- 15 (d) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA) and a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI);
- (e) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI); a CDRL1 comprising SEQ ID NO: 12 (RASQWISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- 20 (f) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI); a CDRL1 comprising SEQ ID NO: 13 (RASQQISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- 25 (g) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI); a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- 30 (h) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 15 (GGIIPIFGIANYA), and a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI);

- 5 (i) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 15 (GGIPIFGIANYA), a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI); a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (CQQSYSTPLTF);
- (j) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 16 (GGIIPNFGTATYA), and a CDRH3 comprising SEQ ID NO: 17 (ARLKGELKGAGDI);
- 10 (k) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 16 (GGIIPNFGTATYA), a CDRH3 comprising SEQ ID NO: 17 (ARLKGELKGAGDI); a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- 15 (l) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), and a CDRH3 comprising SEQ ID NO: 18 (ARLKFELKDAFDI);
- (m) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), a CDRH3 comprising SEQ ID NO: 18 (ARLKFELKDAFDI), a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- 20 (n) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), and a CDRH3 comprising SEQ ID NO: 19 (ARLKGELKDAFDE);
- 25 (o) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), a CDRH3 comprising SEQ ID NO: 19 (ARLKGELKDAFDE), a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- 30 (p) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), and a CDRH3 comprising SEQ ID NO: 20 (ARLKNELKDAFDI);
- (q) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), a CDRH3 comprising SEQ ID NO: 20

- (ARLKNELKDAFDI), a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- 5 (r) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 21 (GGVIPFLGTANYA), and a CDRH3 comprising SEQ ID NO: 22 (ARLKGILKDALDI);
- (s) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 21 (GGVIPFLGTANYA), a CDRH3 comprising SEQ ID NO: 22 (ARLKGILKDALDI), a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a
- 10 CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- (t) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising EQ ID NO: 29 (GRIPIFGTADYA), and a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI);
- 15 (u) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 29 (GRIPIFGTADYA), a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI), a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- 20 (v) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 31 (GGIIPILGTATYA), and a CDRH3 comprising SEQ ID NO: 32 (ARRKGELKDAFDI);
- (w) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 31 (GGIIPILGTATYA), a CDRH3 comprising SEQ ID NO: 32 (ARRKGELKDAFDI), a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a
- 25 CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- (x) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 33 (GGIPIVATANYA), and a CDRH3 comprising SEQ ID NO: 32 (ARRKGELKDAFDI);
- 30 (y) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 33 (GGIPIVATANYA), a CDRH3 comprising SEQ ID NO: 32 (ARRKGELKDAFDI), a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a

CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);

(z) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 34 (GGIPIFGKATYA), and a CDRH3 comprising SEQ ID NO: 32 (ARRKGELKDAFDI);

5 (aa) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 34 (GGIPIFGKATYA), a CDRH3 comprising SEQ ID NO: 32 (ARRKGELKDAFDI), a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);

10 (bb) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI); a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 38 (FQSYSTPLT);

15 (cc) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI); a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 39 (QQSYSTILT);

20 (dd) a CDRH1 comprising SEQ ID NO: 14 (GTFSSYAFS), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA) and a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI); a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);

25 (ee) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), a CDRH2 comprising SEQ ID NO: 24 (GGIPIVGIANYA), and a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI);

(ff) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), a CDRH2 comprising SEQ ID NO: 24 (GGIPIVGIANYA), and a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI); a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);

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- (gg) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), and a CDRH3 comprising SEQ ID NO: 25 (ARLKGEFKDAFDI);
- 5 (hh) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), and a CDRH3 comprising SEQ ID NO: 25 (ARLKGEFKDAFDI); a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- 10 (ii) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), a CDRH2 comprising SEQ ID NO: 26 (GRIIPLFGTAHYA), and a CDRH3 comprising SEQ ID NO: 8 (ARLKGEFKDAFDI);
- (jj) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), a CDRH2 comprising SEQ ID NO: 26 (GRIIPLFGTAHYA), and a CDRH3 comprising SEQ ID NO: 8 (ARLKGEFKDAFDI); a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a
- 15 CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- (kk) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), a CDRH2 comprising SEQ ID NO: 27 (GRINPILGTANYA), and a CDRH3 comprising SEQ ID NO: 28 (ARLKGEFKDAFSI);
- 20 (ll) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), a CDRH2 comprising SEQ ID NO: 27 (GRINPILGTANYA), and a CDRH3 comprising SEQ ID NO: 28 (ARLKGEFKDAFSI); a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);
- 25 (mm) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), and a CDRH3 comprising SEQ ID NO: 30 (ARLKGEFKCAFDI);
- (nn) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), and a comprising SEQ ID NO: 30
- 30 (ARLKGEFKCAFDI); a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT);

(oo) a CDRH1 comprising SEQ ID NO: 36 (GPFRSHAVS), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), and a CDRH3 comprising SEQ ID NO: 37 (ARLKSELKDAFDI); or

(pp) a CDRH1 comprising SEQ ID NO: 36 (GPFRSHAVS), a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), and a CDRH3 comprising SEQ ID NO: 37 (ARLKSELKDAFDI); a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

In some such embodiment examples, the second unit of antigen-binding binds PD-L1 and comprises and comprises a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 35, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, or 58, and a light chain variable region comprising an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 59, 60, 61, 62, or 63.

In some embodiment examples, the second unit of antigen-binding binds PD-L1 and comprises a heavy chain variable region comprising:

- (a) an amino acid sequence that is at least 90% identical to SEQ ID NO: 35;
- (b) an amino acid sequence that is at least 90% identical to SEQ ID NO: 40;
- (c) an amino acid sequence that is at least 90% identical to SEQ ID NO: 41;
- (d) an amino acid sequence that is at least 90% identical to SEQ ID NO: 42;
- (e) an amino acid sequence that is at least 90% identical to SEQ ID NO: 43;
- (f) an amino acid sequence that is at least 90% identical to SEQ ID NO: 44;
- (g) an amino acid sequence that is at least 90% identical to SEQ ID NO: 45;
- (h) an amino acid sequence that is at least 90% identical to SEQ ID NO: 46;
- (i) an amino acid sequence that is at least 90% identical to SEQ ID NO: 47;
- (j) an amino acid sequence that is at least 90% identical to SEQ ID NO: 48;
- (k) an amino acid sequence that is at least 90% identical to SEQ ID NO: 49;
- (l) an amino acid sequence that is at least 90% identical to SEQ ID NO: 50;
- (m) an amino acid sequence that is at least 90% identical to SEQ ID NO: 51;
- (n) an amino acid sequence that is at least 90% identical to SEQ ID NO: 52;
- (o) an amino acid sequence that is at least 90% identical to SEQ ID NO: 53;
- (p) an amino acid sequence that is at least 90% identical to SEQ ID NO: 54;
- (q) an amino acid sequence that is at least 90% identical to SEQ ID NO: 55;
- (r) an amino acid sequence that is at least 90% identical to SEQ ID NO: 56;

- (s) an amino acid sequence that is at least 90% identical to SEQ ID NO: 57; or
- (t) an amino acid sequence that is at least 90% identical to SEQ ID NO: 58;

In some embodimentexamples, the second unit of antigen-binding binds PD-L1 and comprises a light chain variable region comprising:

- (a) an amino acid sequence that is at least 90% identical to SEQ ID NO: 59;
- (b) an amino acid sequence that is at least 90% identical to SEQ ID NO: 60;
- (c) an amino acid sequence that is at least 90% identical to SEQ ID NO: 61;
- (d) an amino acid sequence that is at least 90% identical to SEQ ID NO: 62; or
- (e) an amino acid sequence that is at least 90% identical to SEQ ID NO: 63.

Also provided herein, in some aspectexamples and embodimentexamples, is a multispecific antigen-binding construct comprising four units of antigen-binding, wherein two units of antigen-binding bind PD-1 and two units of antigen-binding bind PD-L1, and wherein the construct comprises a heavy chain amino acid sequence that is at least 85%, identical to the amino acid sequence of SEQ ID NO: 100 or 102, and a light chain amino acid sequence that is at least 85%, identical to the amino acid sequence of SEQ ID NO: 101 or 103.

Also provided herein, in some aspectexamples and embodimentexamples, is a multispecific antigen-binding construct comprising four units of antigen-binding, wherein two units of antigen-binding bind PD-1 and two units of antigen-binding bind PD-L1, and wherein the construct comprises a heavy chain amino acid sequence that is at least 85%, identical to the amino acid sequence of SEQ ID NO: 100 and a light chain amino acid sequence that is at least 85%, identical to the amino acid sequence of SEQ ID NO: 101.

Also provided herein, in some aspectexamples and embodimentexamples, is a multispecific antigen-binding construct comprising four units of antigen-binding, wherein two units of antigen-binding bind PD-1 and two units of antigen-binding bind PD-L1, and wherein the construct comprises a heavy chain amino acid sequence that is at least 85%, identical to the amino acid sequence of SEQ ID NO: 102 and a light chain amino acid sequence that is at least 85%, identical to the amino acid sequence of SEQ ID NO: 103.

In some embodimentexamples, the construct does not comprise an Fc domain. In some embodimentexamples, the first arm or second arm, or both, comprises a heavy chain comprising one or more immunoglobulin Fc modifications. In some embodimentexamples, the immunoglobulin Fc domain of the heavy chain comprises one or more amino acid mutations that promote heterodimerization of the first and second arms. In some embodimentexamples, the mutation is present in a CH3 domain of the heavy chain. In some embodimentexamples, the multispecific antigen-binding construct is produced in a quadroma cell. In some embodimentexamples, the

construct comprises one or more immunoglobulin constant region modifications. In some [embodimentexamples](#), the immunoglobulin constant region comprises one or more amino acid mutations that promote heterodimerization of antibodies. In some [embodimentexamples](#), one or more mutations is present in the light chain constant region of one arm and one or more mutations is present in the heavy chain constant region of another arm. In some [embodimentexamples](#), the bispecific antibody is of a format selected from the group consisting of a bispecific IgG, bispecific antibody fragment, bispecific fusion protein, appended IgG, and bispecific antibody conjugate. In some [embodimentexamples](#), the Fc region has reduced effector function. In some [embodimentexamples](#), the Fc region enhances half-life of the construct.

In some [embodimentexamples](#), the construct comprises a heavy chain amino acid sequence that is at least 85%, identical to the amino acid sequence of SEQ ID NO: 100 or 102. In some [embodimentexamples](#), the construct comprises a light chain amino acid sequence that is at least 85%, identical to the amino acid sequence of SEQ ID NO: 101 or 103. In some [embodimentexamples](#), the construct comprises a heavy chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 100, and wherein the construct comprises a light chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 101. In some [embodimentexamples](#), the construct comprises a heavy chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 102, and wherein the construct comprises a light chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 103.

In some [embodimentexamples](#), any of the multispecific antigen-binding constructs disclosed herein are aglycosylated. In some [embodimentexamples](#), the multispecific antigen-binding construct is capable of binding human PD-1. In some [embodimentexamples](#), the multispecific antigen-binding construct is capable of binding murine PD-1. In some [embodimentexamples](#), the multispecific antigen-binding construct is capable of binding cynomolgus monkey PD-1. In some [embodimentexamples](#), the multispecific antigen-binding construct is capable of binding human, murine and cynomolgus monkey PD-1 with similar affinity.

In some [embodimentexamples](#), any of the multispecific antigen-binding constructs disclosed herein is capable of reducing PD-1 levels on a cell. In some [embodimentexamples](#), the multispecific antigen-binding construct is capable of inducing PD-1 degradation. In some [embodimentexamples](#), the multispecific antigen-binding construct is capable of reducing PD-1 expression. In some [embodimentexamples](#), the multispecific antigen-binding construct is capable of reducing PD-1 cell surface expression. In some [embodimentexamples](#), the multispecific antigen-binding construct is capable of reducing PD-1 cell surface expression by inducing shedding of PD-1 from the cell

surface. In some embodimentexamples, the multispecific antigen-binding construct is capable of binding both PD-1 and PD-L1 and reducing PD-1 levels on a cell. In some embodimentexamples, the multispecific antigen-binding construct is capable of binding both PD-1 and PD-L1 and inducing PD-1 degradation. In some embodimentexamples, the multispecific antigen-binding construct is capable of binding both PD-1 and PD-L1 and reducing PD-1 expression. In some embodimentexamples, the multispecific antigen-binding construct is capable of inducing shedding of PD-1 from an immune cell. In some embodimentexamples, the multispecific antigen-binding construct is capable of binding both PD-1 and PD-L1 and inducing PD-1 shedding from an immune cell. In some embodimentexamples, the multispecific antigen-binding construct is capable of sequestering PD-L1, such that PD-L1 cannot bind CD80. In some embodimentexamples, the multispecific antigen-binding construct is capable of sequestering PD-L1, such that PD-L1 cannot bind CD80, and wherein CD80 is free to bind CD28. In some embodimentexamples, the cell is an immune cell, such as a T cell. In some embodimentexamples, the immune cell (e.g., T cell) is a tumor infiltrating lymphocyte (TIL). In some embodimentexamples, engagement of a multispecific antigen-binding molecule described herein to PD-1 expressed by an immune cell in the tumor microenvironment results in the downregulation of PD-1 by the immune cell. In some embodimentexamples, the immune cell is a T cell. In some embodimentexamples, the immune cell (e.g., T cell) is a tumor infiltrating lymphocyte (TIL).

In some embodimentexamples, any of the multispecific antigen-binding constructs disclosed herein is capable of inducing at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 99% greater interferon-gamma levels (e.g., as measured in a *Staphylococcus aureus* Enterotoxin A (“SEA”) assay) as compared to a reference antigen-binding construct (e.g., pembrolizumab or atezolizumab) or to a reference combination of antigen-binding constructs (e.g., a composition comprising the PD-1 and PD-L1 arms of the multispecific antigen-binding construct, wherein the PD-1 and PD-L1 arms in the composition are not conjugated to one another). In some embodimentexamples, the multispecific antigen-binding construct is capable of inducing at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 99% greater interleukin-2 levels (e.g., as measured in a SEA assay) as compared to a reference antigen-binding construct (e.g., pembrolizumab or atezolizumab) or to a reference combination of antigen-binding constructs (e.g., a composition comprising the PD-1 and PD-L1 arms of the multispecific antigen-binding construct, wherein the PD-1 and PD-L1 arms in the composition are not conjugated to one another).

In some embodiment examples, the multispecific antigen-binding construct induces at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, 200%, 300%, 400%, or 500% more killing of tumor cells (*e.g.*, leukemia cells, lymphoma cells, melanoma, or breast cancer cells), as compared to a reference antigen-binding construct (*e.g.*, pembrolizumab or atezolizumab) or to a reference combination of antigen-binding constructs (*e.g.*, a composition comprising the PD-1 and PD-L1 arms of the multispecific antigen-binding construct, wherein the PD-1 and PD-L1 arms in the composition are not conjugated to one another).

In some embodiment examples, the multispecific antigen-binding construct is capable of extending the survival of a subject suffering from a cancer (*e.g.*, leukemia, lymphoma, melanoma, and/or breast cancer) by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, 100%, 200%, 300%, 400%, or 500% longer than a subject administered a reference antigen-binding construct (*e.g.*, pembrolizumab or atezolizumab) or a reference combination of antigen-binding constructs (*e.g.*, a composition comprising the PD-1 and PD-L1 arms of the multispecific antigen-binding construct, wherein the PD-1 and PD-L1 arms in the composition are not conjugated to one another). In some embodiment examples, the multispecific antigen-binding construct is capable of inducing at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, 100%, 200%, 300%, 400%, or 500% more shedding of PD-1 from an immune cell as compared to an untreated immune cell or as compared to an immune cell treated with reference antigen-binding construct (*e.g.*, pembrolizumab or atezolizumab) or a reference combination of antigen-binding constructs (*e.g.*, a composition comprising the PD-1 and PD-L1 arms of the multispecific antigen-binding construct, wherein the PD-1 and PD-L1 arms in the composition are not conjugated to one another). In some embodiment examples, the multispecific antigen-binding construct is capable of reducing PD-1 levels at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, 100%, 200%, 300%, 400%, or 500% (*e.g.*, by causing PD-1 shedding from the cell surface and/or inducing PD-1 degradation and/or reducing PD-1 expression) as compared to an untreated immune cell or to an immune cell treated with a reference antigen-binding construct (*e.g.*, pembrolizumab or atezolizumab) or a reference combination of antigen-binding constructs (*e.g.*, a composition comprising the PD-1 and PD-L1 arms of the multispecific antigen-binding construct, wherein the PD-1 and PD-L1 arms in the composition are not conjugated to one another).

In some embodimentexamples, engagement of a multispecific antigen-binding molecule described herein to PD-1 expressed by a cell results in the downregulation and/or loss of cell-surface expression of PD-1 by the cell. Such down-regulation or loss of cell-surface expression can be due to, in part, for example, shedding of extracellular PD-1 from the surface of the immune cell. In some embodimentexamples, the cell is an immune cell, such as a T cell. In some embodimentexamples, the immune cell (e.g., T cell) is a tumor infiltrating lymphocyte (TIL). In some embodimentexamples, engagement of a multispecific antigen-binding molecule described herein to PD-1 expressed by an immune cell in the tumor microenvironment results in the downregulation of PD-1 by the immune cell. In some embodimentexamples, the immune cell is a T cell. In some embodimentexamples, the immune cell (e.g., T cell) is a tumor infiltrating lymphocyte (TIL).

In some aspectexamples, the disclosure provides for a method for treating a proliferative disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of any of the multispecific antigen-binding constructs disclosed herein, thereby treating the proliferative disorder in the subject. In some embodimentexamples, the proliferative disorder is cancer. In some embodimentexamples, the cancer is selected from the group consisting of a hematological cancer, a neurological cancer, melanoma, breast cancer, lung cancer, head and neck cancer, a gastrointestinal cancer, liver cancer, pancreatic cancer, a genitourinary cancer, a bone cancer, and a vascular cancer. In some embodimentexamples, the disclosure provides for a method of enhancing an immune response in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of any of the multispecific antigen-binding constructs disclosed herein, thereby enhancing the immune response in the subject. In some embodimentexamples, the enhanced immune response includes any one or more of enhanced T cell function, enhanced NK cell function, or enhanced macrophage function. In some embodimentexamples, the enhancement of T cell function is greater upon administration of the multispecific antigen-binding construct, as compared to an agent that binds either PD-1 or a PD-1 ligand, or a cocktail comprising an agent that binds PD-1 and an agent that binds a PD-1 ligand. In some embodimentexamples, the T cell function is any one or more of increased IFN γ production from T cells, enhanced T cell survival, increased T cell proliferation, or rescue from an exhausted T cell phenotype. In some embodimentexamples, the enhanced T cell function is greater upon administration of the multispecific antigen-binding construct, as compared to an agent that binds either PD-1 or a PD-1 ligand, or a cocktail comprising an agent that binds PD-1 and an agent that binds a PD-1 ligand. In some

embodimentexamples, the multispecific antigen-binding construct is administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, intramuscularly or intracranially. In some embodimentexamples, the multispecific antigen-binding construct binds to PD-1 and to PD-L1 expressed on the surface of the same cell in the subject. In some embodimentexamples, the multispecific antigen-binding construct binds to PD-1 expressed on the surface of a first cell in the subject, and wherein the multispecific antigen-binding construct binds to PD-L1 expressed on the surface of a second cell in the subject.

In some embodimentexamples, the disclosure provides for an anti-PD1 antibody or antigen-binding fragment thereof, wherein the anti-PD-1 antibody or antigen-binding fragment comprises: (a) a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 70 (FTFX₁X₂YAX₃X₄, wherein X₁=S, R, G, or N; X₂=D, S, N, A, R, or G; X₃= M or L; X₄= S, L, or N); (ii) a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYYA); and (iii) a CDRH3 comprising SEQ ID NO: 72 (ARGLDFIVGX₅TGNDY, wherein X₅=A, Y, or R); and (b) a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT). In some embodimentexamples, the anti-PD-1 antibody or antigen-binding fragment comprises: (a) a heavy chain variable region comprising (i) a CDRH1 comprising the amino acid sequence of any one of SEQ ID NOs: 73, 76, 77, 78, 79, 80, 81, 82, 83, 84, or 86; (ii) a CDRH2 comprising the amino acid sequence of SEQ ID NO: 71; and (iii) a CDRH3 comprising the amino acid sequence of any one of SEQ ID NOs: 74, 75, or 85; and (b) a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT). In some embodimentexamples, the heavy chain variable region comprises an amino acid sequence that is at least 85% identical to the amino acid sequence of any one of SEQ ID NOs: 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99. In some embodimentexamples, the light chain variable region comprises an amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 59.

In some embodimentexamples, the disclosure provides for an anti-PD-L1 antibody or antigen-binding fragment thereof, wherein the anti-PD-L1 antibody or antigen-binding fragment comprises: a. a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN); (ii) a CDRH2 comprising SEQ ID NO: 2 (GGIIPX₁X₂GX₃ATYA, wherein X₁ is V or I; X₂ is F, L, or V; and X₃ is T or A); and (iii) a CDRH3 comprising SEQ ID NO: 3 (ARLKX₁ELKDAFDI, wherein X₁ is G, F, or N); and b. a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 4 (RASQX₁ISSYLN, wherein X₁ is

S, W, or Q); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 6 (X₁QSYSTPLT, wherein X₁ is Q or F). In some

embodimentexamples, the anti-PD-L1 antibody or antigen-binding fragment comprises: (a) a heavy chain variable region comprising (i) a CDRH1 comprising the amino acid sequence of any one of SEQ ID NOs: 1, 14, 23, 36, or 122; (ii) a CDRH2 comprising the amino acid sequence of any one of SEQ ID NOs: 11, 15, 16, 21, 24, 26, 27, 29, 31, 33, or 34; and (iii) a CDRH3 comprising the amino acid sequence of any one of SEQ ID NOs: 8, 17, 18, 19, 20, 22, 25, 28, 30, 32, or 37; and (b) a light chain variable region comprising: (i) a CDRL1 comprising the amino acid sequence of any one of SEQ ID NOs: 9, 12, or 13; (ii) a CDRL2 comprising the amino acid sequence of SEQ ID NO: 5; and (iii) a CDRL3 comprising the amino acid sequence of any one of SEQ ID NOs: 10, 38 or 39. In some embodimentexamples, the heavy chain variable region comprises an amino acid sequence that is at least 85% identical to the amino acid sequence of any one of SEQ ID NOs: 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 35. In some embodimentexamples, the light chain variable region comprises an amino acid sequence that is at least 85% identical to the amino acid sequence of any one of SEQ ID NOs: 59, 60, 61, 62, or 63.

In some embodimentexamples, the disclosure provides for a method for treating a proliferative disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of any of the antibodies or antigen-binding constructs disclosed herein, thereby treating the proliferative disorder in the subject. In some embodimentexamples, the proliferative disorder is cancer. In some embodimentexamples, the cancer is selected from the group consisting of a hematological cancer, a neurological cancer, melanoma, breast cancer, lung cancer, head and neck cancer, a gastrointestinal cancer, liver cancer, pancreatic cancer, a genitourinary cancer, a bone cancer, and a vascular cancer.

In some embodimentexamples, the disclosure provides for a method of enhancing an immune response in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of any of the antibodies or antigen-binding constructs disclosed herein, thereby enhancing the immune response in the subject.

In some embodimentexamples, any of the methods described herein can involve detecting the presence or absence of PD-1 expression by one or more cells (or a population of cells, such as TILs) before and/or after contact with a multispecific antigen-binding molecule described herein. For example, any of the methods described herein can involve detecting the presence or absence of PD-1 expression by one or more cells (or a population of cells, such as TILs) before and/or after administration of a multispecific antigen-binding molecule described

herein to a subject (e.g., a cancer patient). Such methods are useful, e.g., determining a therapeutically effective amount of the molecule for use in treatment of a given patient or patient population. Methods of detecting the presence, reduction in expression, and/or absence of PD-1 expression are known to those of skill in the art, for example, using flow cytometry, Western blotting, ELISA, etc.

In another [aspectexample](#), the disclosure features a method comprising measuring the level of PD-1 expression by one or more cells (or a population of cells, such as TILs) before and/or after contact with a multispecific antigen-binding molecule described herein. In some [embodimentexamples](#), the method comprises measuring the level of PD-1 expression by one or more cells (or a population of cells, such as TILs) before and/or after administration of a multispecific antigen-binding molecule described herein to a subject (e.g., a cancer patient).

In yet another [aspectexample](#), the disclosure features a method comprising measuring the level of PD-1 expression by one or more cells (or a population of cells, such as TILs) before and/or after contact with a multispecific antigen-binding molecule described herein.

For example, any of the methods described herein can involve measuring the level of PD-1 expression by one or more cells (or a population of cells, such as TILs) before and/or after administration of a multispecific antigen-binding molecule described herein to a subject (e.g., a cancer patient). Such methods are useful for, among other things, detecting or measuring a biological effect of a molecule described herein on the subject. In some

[embodimentexamples](#), a reduction in the level of PD-1 expression by an immune cell (e.g., TILs isolated from a patient) following treatment with a multispecific antigen-binding molecule described herein indicates that the molecule has had a biological effect in the subject. In some [embodimentexamples](#), a reduction in the level of PD-1 expression by an immune cell (e.g., TILs isolated from a patient) following treatment with a multispecific antigen-binding molecule described herein indicates that the patient should receive one or more doses of the molecule, or otherwise continue on a therapy comprising the molecule.

In yet another [aspectexample](#), the disclosure features methods for determining whether a biological effect has occurred in a patient or population of patients treated with a multispecific antigen-binding molecule described herein. The method comprises detecting the presence or amount of PD-1 expression by one or more test immune cells (e.g., effector immune cells, such as those in the tumor microenvironment) obtained from a patient or patients who have been administered a multispecific antigen-binding molecule described herein, wherein a reduced level of PD-1 expression (e.g., cell surface expression) of PD-1 by the one or more immune cells relative to a control expression level (e.g., the expression level

of PD-1 by immune cells of the same histological type as the test immune cells prior to administration of the molecule) indicates that a biological effect has occurred in the patient or population of patients. In some embodimentexamples, the method comprises administering the multispecific antigen-binding molecule prior to the detecting. In some embodimentexamples, the method comprises administering a multispecific antigen-binding molecule to the patient or population of patients in whom the occurrence of a biological effect has been determined. In some embodimentexamples, control PD-1 expression level is approximately the median or average expression level of PD-1 by immune cells of the same histological type in a population of subjects who have not been diagnosed as having a cancer. In some embodimentexamples, control PD-1 expression level is approximately the median or average expression level of PD-1 by immune cells of the same histological type in a population of subjects who have not been administered a multispecific antigen-binding molecule described herein and/or an agent that binds to and/or inhibits PD-1.

In yet another aspectexample, the disclosure features a method for reducing the expression of PD-1 by one or more immune cells in a subject (*e.g.*, a cancer patient), the method comprising administering a multispecific antigen-binding molecule described herein to a subject to thereby reduce the expression of PD-1 by one or more immune cells in the subject. In some embodimentexamples, the method comprises determining whether a reduction in PD-1 expression by one or more immune cells in the patient has occurred. In some embodimentexamples, the method comprises obtaining from the subject a biological sample (*e.g.*, a tumor biopsy) comprising one or more immune cells (*e.g.*, after administration of the molecule to the subject). In some embodimentexamples, the method comprises measuring the level of PD-1 expression by one or more immune cells in the biological sample.

In yet another aspectexample, the disclosure features a method for inhibiting binding between PD-L1 and CD80 in a subject (*e.g.*, a cancer patient), the method comprising administering a multispecific antigen-binding molecule described herein to a subject to thereby inhibit binding between PD-L1 and CD80 in the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Figure 1 shows the induction of interferon-gamma (IFN γ) in a mixed lymphocyte reaction (MLR) assay treated with various antibody cocktails or bispecific antibodies

WE CLAIM:

1. A multispecific antigen-binding construct comprising at least two antigen-binding arms, wherein:

5 _____ a first arm binds PD-1 and comprises a heavy chain variable region and a light chain variable region, the heavy chain variable region of the first arm comprising a CDRH1 of SEQ ID NO: 77, a CDRH2 of SEQ ID NO: 71, and a CDRH3 of SEQ ID NO: 75 expressed by an immune cell, and

10 _____ a second arm binds a PD-1 ligand and comprises a heavy chain variable region and a light chain variable region, the heavy chain variable region of the second arm comprising a CDRH1 of SEQ ID NO: 1, a CDRH2 of SEQ ID NO: 7, and a CDRH3 of SEQ ID NO: 8;

15 _____ wherein the light chain variable region of the first arm and the light chain variable region of the second arm each comprise a CDRL1 of SEQ ID NO: 9, a CDRL2 of SEQ ID NO: 5, and a CDRL3 of SEQ ID NO: 10; and ~~which is expressed by a second cell,~~

_____ wherein the multispecific antigen-binding construct blocks the interaction of PD-1 and PD-1 ligand.

20 ~~2. The multispecific antigen-binding construct of claim 1, wherein the PD-1 ligand is PD-L2.~~

~~3. The multispecific antigen-binding construct of claim 1, wherein the PD-1 ligand is PD-L1.~~

25 ~~4. The multispecific antigen-binding construct of any one of claims 1-3, wherein the immune cell is a T cell.~~

~~5. The multispecific antigen-binding construct of claim 4, wherein the T cell is a CD8+ T cell.~~

30 ~~6. The multispecific antigen-binding construct of any one of claims 1-3, wherein the immune cell is a natural killer (NK) cell.~~

7. — ~~The multispecific antigen-binding construct of any one of claims 1-3, wherein the immune cell is a macrophage.~~

8. — ~~The multispecific antigen-binding construct of any one of claims 1-6, wherein the second cell is a second immune cell.~~

9. — ~~The multispecific antigen-binding construct of claim 8, wherein the second immune cell is any one or more of a T cell, a B cell, a macrophage, a myeloid-derived suppressor cell, a dendritic cell, or a mesenchymal stromal cell.~~

10. — ~~The multispecific antigen-binding construct of claim 9, wherein the second immune cell is a regulatory T cell.~~

11. — ~~The multispecific antigen-binding construct of any one of claims 1-7, wherein the second cell is a tumor cell.~~

12. — ~~The multispecific antigen-binding construct of claim 11, wherein the tumor cell is selected from the group consisting of a hematological cancer, a lymphoma, a myeloma, a leukemia, a neurological cancer, melanoma, breast cancer, a prostate cancer, a colorectal cancer, lung cancer, head and neck cancer, a gastrointestinal cancer, liver cancer, pancreatic cancer, a genitourinary cancer, a bone cancer, renal cancer, and a vascular cancer.~~

13. — ~~The multispecific antigen-binding construct of any one of claims 1-12, wherein both arms have a K_D of at least 1×10^{-7} M, at least 1×10^{-8} M, at least 1×10^{-9} M, or at least 1×10^{-10} M.~~

14. — ~~The multispecific antigen-binding construct of any one of claims 1-13, wherein the binding of one arm to its target does not block the binding of the other arm to its target.~~

15. — ~~The multispecific antigen-binding construct of any one of claims 1-14, wherein the first arm and second arm bind to their respective targets and both arms remain bound concurrently.~~

16.—The multispecific antigen-binding construct of any one of claims 1-15, wherein binding of the first arm and the second arm to their respective targets can bridge the immune cell and the second cell together.

17.—The multispecific antigen-binding construct of claim 16, wherein the bridging of the immune cell and the second cell is determined by flow cytometry.

18.—The multispecific antigen-binding construct of any one of claims 1-17, wherein the first arm is an antagonist of PD-1.

19.—The multispecific antigen-binding construct of claim 18, wherein the first arm comprises:

(a) a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 70 (FTFX₁X₂YAX₃X₄, wherein X₁=S, R, G, or N; X₂=D, S, N, A, R, or G; X₃=M or L; X₄=S, L, or N); (ii) a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYYA); and (iii) a CDRH3 comprising SEQ ID NO: 72 (ARGLDFIVGX₅YGNDY, wherein X₅=A, Y, or R); and

(b) a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

20.—The multispecific antigen-binding construct of claim 19, wherein CDRH1 of the first arm comprises SEQ ID NO: 73 (FTFSDYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA), and CDRH3 of the first arm comprises SEQ ID NO: 74 (ARGLDFIVGATGNDY).

21.—The multispecific antigen-binding construct of claim 19, wherein CDRH1 of the first arm comprises SEQ ID NO: 73 (FTFSDYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA), and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY).

22.—The multispecific antigen-binding construct of claim 19, wherein CDRH1 of the first arm comprises SEQ ID NO: 76 (FTFSSYAMS), CDRH2 of the first arm comprises SEQ ID

NO: 71 (SAISNSGTYTYYA), and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY).

23. — The multispecific antigen-binding construct of claim 19, wherein CDRH1 of the first arm comprises SEQ ID NO: 77 (FTFSSYAML), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA), and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY).

24. — The multispecific antigen-binding construct of claim 19, wherein CDRH1 of the first arm comprises SEQ ID NO: 78 (FTFSNYALS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA), and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY).

25. — The multispecific antigen-binding construct of claim 19, wherein CDRH1 of the first arm comprises SEQ ID NO: 79 (FTFSAYAMN), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA), and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY).

26. — The multispecific antigen-binding construct of claim 19, wherein CDRH1 of the first arm comprises SEQ ID NO: 80 (FTFRSYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA), and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY).

27. — The multispecific antigen-binding construct of claim 19, wherein CDRH1 of the first arm comprises SEQ ID NO: 81 (FTFGRYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA), and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY).

28. — The multispecific antigen-binding construct of claim 19, wherein CDRH1 of the first arm comprises SEQ ID NO: 82 (FTFNSYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA), and CDRH3 of the first arm comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY).

29.—The multispecific antigen-binding construct of claim 19, wherein CDRH1 of the first arm comprises SEQ ID NO: 83 (FTFSNYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA), and CDRH3 of the first arm comprises SEQ ID NO: 74 (ARGLDFIVGATGNDY).

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30.—The multispecific antigen-binding construct of claim 19, wherein CDRH1 of the first arm comprises SEQ ID NO: 84 (FTFSGYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA), and CDRH3 of the first arm comprises SEQ ID NO: 85 (ARGLDFIVGRTGNDY).

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31.—The multispecific antigen-binding construct of claim 19, wherein CDRH1 of the first arm comprises SEQ ID NO: 86 (FTFSSYAMN), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA) and CDRH3 of the first arm comprises SEQ ID NO: 85 (ARGLDFIVGRTGNDY).

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32.—The multispecific antigen-binding construct of claim 19, wherein CDRH1 of the first arm comprises SEQ ID NO: 80 (FTFRSYAMS), CDRH2 of the first arm comprises SEQ ID NO: 71 (SAISNSGTYTYYA), and CDRH3 of the first arm comprises SEQ ID NO: 85 (ARGLDFIVGRTGNDY).

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33.—The multispecific antigen-binding construct of claim 19, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 87.

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34.—The multispecific antigen-binding construct of claim 19, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 88.

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35.—The multispecific antigen-binding construct of claim 19, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 89.

2. The multispecific antigen-binding construct of claim 1, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 85% identical to SEQ ID NO: 90.

5 363. The multispecific antigen-binding construct of claim 191, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 90.

10 4. The multispecific antigen-binding construct of claim 1, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 55.

15 ~~37.—The multispecific antigen-binding construct of claim 19, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 91.~~

20 ~~38.—The multispecific antigen-binding construct of claim 19, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 92.~~

~~39.—The multispecific antigen-binding construct of claim 19, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 93.~~

25 ~~40.—The multispecific antigen-binding construct of claim 19, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 94.~~

30 ~~41.—The multispecific antigen-binding construct of claim 19, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 95.~~

42.—The multispecific antigen-binding construct of claim 19, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 96.

43.—The multispecific antigen-binding construct of claim 19, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 97.

44.—The multispecific antigen-binding construct of claim 19, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 98.

45.—The multispecific antigen-binding construct of claim 19, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 99.

46.—The multispecific antigen-binding construct of any one of claims 19-45, wherein the light chain variable region of the first arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 59.

47.—The multispecific antigen-binding construct of any one of claims 1-46, wherein the second arm is an antagonist of the PD-1 ligand.

48.—The multispecific antigen-binding construct of any one of claims 1-47, wherein the second arm is an antagonist of PD-L2.

49.—The multispecific antigen-binding construct of any one of claims 1-47, wherein the second arm is an antagonist of PD-L1.

50.—The multispecific antigen-binding construct of claim 49, wherein the second arm comprises:

- a.—a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN); (ii) a CDRH2 comprising SEQ ID NO: 2 (GGIIPX₁X₂GX₃ATYA;

wherein X_1 is V or I; X_2 is F, L, or V; and X_3 is T or A); and (iii) a CDRH3 comprising SEQ ID NO: 3 (ARLK X_4 ELKD X_5 AFDI, wherein X_4 is G, F, or N); and
b. — a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 4 (RASQ X_6 ISSYLN, wherein X_6 is S, W, or Q); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 6 (X_7 QSYSTPLT, wherein X_7 is Q or F).

51. — The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 7 (GGHIPILGAATYA), and CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKD X_8 AFDI).

52. — The multispecific antigen-binding construct of claim 51, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 7 (GGHIPILGAATYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKD X_9 AFDI); CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

53. — The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGHIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKD X_{10} AFDI); CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

54. — The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGHIPVFGTATYA) and CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKD X_{11} AFDI).

55. — The multispecific antigen-binding construct of claim 54, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGHIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 8

(ARLKGELKDAFDI); CDRL1 of the second arm comprises SEQ ID NO: 12 (RASQWISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

56.—The multispecific antigen-binding construct of claim 54, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second arm comprises SEQ ID NO: 13 (RASQQISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

57.—The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

58.—The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 15 (GGIIPIFGIANYA), and CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI).

59.—The multispecific antigen-binding construct of claim 58, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 15 (GGIIPIFGIANYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

60.—The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 16 (GGIIPNFGTATYA), and CDRH3 of the second arm comprises SEQ ID NO: 17 (ARLKGELKGAGDI).

61. — The multispecific antigen-binding construct of claim 60, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 16 (GGIIPNFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 17 (ARLKGELKGAGDI); CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

62. — The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), and CDRH3 of the second arm comprises SEQ ID NO: 18 (ARLKFELKDADFID).

63. — The multispecific antigen-binding construct of claim 62, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 18 (ARLKFELKDADFID), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

64. — The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), and CDRH3 of the second arm comprises SEQ ID NO: 19 (ARLKGELKDADFDE).

65. — The multispecific antigen-binding construct of claim 64, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 19 (ARLKGELKDADFDE), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

66. — The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises

SEQ ID NO: 11 (GGHIPVFGTATYA), and CDRH3 of the second arm comprises SEQ ID NO: 20 (ARLKNELKDAFDI).

67. — The multispecific antigen-binding construct of claim 66, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGHIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 20 (ARLKNELKDAFDI), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

68. — The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 21 (GGVIPFLGTANYA), and CDRH3 of the second arm comprises SEQ ID NO: 22 (ARLKGILKDALDI).

69. — The multispecific antigen-binding construct of claim 68, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 21 (GGVIPFLGTANYA), CDRH3 of the second arm comprises SEQ ID NO: 22 (ARLKGILKDALDI), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

70. — The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 29 (GRIPIFGTADYA), and CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI).

71. — The multispecific antigen-binding construct of claim 70, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 29 (GRIPIFGTADYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

72.—The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 31 (GGIIPILGTATYA), and CDRH3 of the second arm comprises SEQ ID NO: 32 (ARRKGELKDAFDI).

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73.—The multispecific antigen-binding construct of claim 72, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 31 (GGIIPILGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 32 (ARRKGELKDAFDI), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

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74.—The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 33 (GGIPIVATANYA), and CDRH3 of the second arm comprises SEQ ID NO: 32 (ARRKGELKDAFDI).

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75.—The multispecific antigen-binding construct of claim 74, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 33 (GGIPIVATANYA), CDRH3 of the second arm comprises SEQ ID NO: 32 (ARRKGELKDAFDI), CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

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76.—The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 34 (GGIPIFGKATYA), and CDRH3 of the second arm comprises SEQ ID NO: 32 (ARRKGELKDAFDI).

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77.—The multispecific antigen-binding construct of claim 76, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 34 (GGIPIFGKATYA), CDRH3 of the second arm comprises SEQ ID NO: 32 (ARRKGELKDAFDI), CDRL1 of the second arm comprises SEQ ID NO: 9

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(RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 10 (QQSYSTPLT).

78. — The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 38 (FQSYSTPLT).

79. — The multispecific antigen-binding construct of claim 50, wherein CDRH1 of the second arm comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second arm comprises SEQ ID NO: 11 (GGIIPVFGTATYA), CDRH3 of the second arm comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second arm comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second arm comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second arm comprises SEQ ID NO: 39 (QQSYSTILT).

80. — The multispecific antigen-binding construct of claim 50, wherein the second arm comprises:

a. — a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 14 (GTFSSYAFA), (ii) a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA) and (iii) a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI); and

b. — a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

81. — The multispecific antigen-binding construct of claim 50, wherein the second arm comprises a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 23 (GTFSSYAIS), (ii) a CDRH2 comprising SEQ ID NO: 24 (GGIPIVGIANYA), and (iii) a CDRH3 comprising SEQ ID NO: 8 (ARLKGELKDAFDI).

82. — The multispecific antigen-binding construct of claim 81, wherein the second arm comprises a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9

(RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QSYSTPLT).

83. — The multispecific antigen-binding construct of claim 50, wherein the second arm comprises a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), (ii) a CDRH2 comprising SEQ ID NO: 11 (GGIIPVFGTATYA), and (iii) a CDRH3 comprising SEQ ID NO: 25 (ARLKGEFKDAFDI).

84. — The multispecific antigen-binding construct of claim 83, wherein the second arm comprises a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QSYSTPLT).

85. — The multispecific antigen-binding construct of claim 50, wherein the second arm comprises a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), (ii) a CDRH2 comprising SEQ ID NO: 26 (GRIPLFGTAHYA), and (iii) a CDRH3 comprising SEQ ID NO: 8 (ARLKGE LKDAFDI).

86. — The multispecific antigen-binding construct of claim 85, wherein the second arm comprises a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QSYSTPLT).

87. — The multispecific antigen-binding construct of claim 50, wherein the second arm comprises a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), (ii) a CDRH2 comprising SEQ ID NO: 27 (GRINPILGTANYA), and (iii) a CDRH3 comprising SEQ ID NO: 28 (ARLKGE LKDAFSI).

88. — The multispecific antigen-binding construct of claim 87, wherein the second arm comprises a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QSYSTPLT).

89.—The multispecific antigen-binding construct of claim 50, wherein the second arm comprises a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 23 (GTFSSY AIS), (ii) a CDRH2 comprising SEQ ID NO: 11 (GGHPVFGTATYA), and (iii) a CDRH3 comprising SEQ ID NO: 30 (ARLKGELKCAFDI).

90.—The multispecific antigen-binding construct of claim 89, wherein the second arm comprises a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QSYSTPLT).

91.—The multispecific antigen-binding construct of claim 50, wherein the second arm comprises a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 36 (GPFRSHAVS), (ii) a CDRH2 comprising SEQ ID NO: 11 (GGHPVFGTATYA), and (iii) a CDRH3 comprising SEQ ID NO: 37 (ARLKSELKD AFDI).

92.—The multispecific antigen-binding construct of claim 91, wherein the second arm comprises a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QSYSTPLT).

93.—The multispecific antigen-binding construct of claim 50, wherein the second arm comprises a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 35, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, or 58, and a light chain variable region comprising an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 59, 60, 61, 62, or 63.

94.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 35
(QVQLVQSGAEVKKPGSSVKV SCKASGGTFSSYAINWVRQAPGQGLEWMGGHPVFGTATY A QKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARLKGELKD AFDI WGG GTMVT VSS).

95.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 40

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAFSWVRQAPGQGLEWMGGHIPVF
GTATYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARLKGELKDAFDIWG
QGTLVTVSS).

96.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 41

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAINWVRQAPGQGLEWMGGHIPFGI
ANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARLKGELKDAFDIWGQG
TLVTVSS).

97.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 42

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAINWVRQAPGQGLEWMGGHIPNFG
TATYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARLKGELKGAGDIWGQ
GTLVTVSS).

98.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 43

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAINWVRQAPGQGLEWMGGHIPVFG
TATYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARLKFELKDAFDIWGQG
TLVTVSS).

99.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 44

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAINWVRQAPGQGLEWMGGHIPVFG
TATYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARLKGELKDAFDEWGQ
GTLVTVSS).

100.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 45

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAINWVRQAPGQGLEWMGGHIPVFG
TATYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARLKGELKDAFDIWGQ
GTLVTAST).

101.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 46

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAINWVRQAPGQGLEWMGGHIPVFG
TATYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARLKNELKDAFDIWGQ
GTLVTVSS).

102.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 47

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAINWVRQAPGQGLEWMGGVIPFL
GTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARLKGILKDALDIWG
QGTLVTVSS).

103.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 48

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQDLEWMGGHIPVGI
ANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARLKGELKDAFDIWGQG
TLVTVSS).

104.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 49

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGHIPVFG
TATYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARLKGFEKDAFDIWGQ
GTLVTVSS).

105.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 50

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGRIPLFGTAHYAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARLKGELKDAFDIWGQGTLVTVSS).

106.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 51

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGRINPILGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARLKGELKDAFSIWGQGTLVTVSS).

107.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 52

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAINWVRQAPGQGLEWMGRIPIFGTADY AQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARLKGELKDAFDIWGQGTLVTVSS).

108.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 53

(QVQLVQSGAEVKKPGSSVKVSCKASGGKFSSYAISWVRQAPGQGLEWMGGHIPVFGTATY AQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARLKGELKCAFDIWGQGTLVTVSS).

109.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 54

(QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAINWVRQAPGQGLEWMGGHIPILG

TATYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARRKGELKDAFDIWGQ
GTLVTVSS).

1105. The multispecific antigen-binding construct of claim 931, wherein the heavy chain
variable region of the second arm comprises an amino acid sequence that is at least 90%
identical to SEQ ID NO: 55

(QVQLVQSGAEVKKPGSSVKV SCKASGGTFSSYAINWVRQAPGQGLEWMGGHIPILG
AATYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARLKGELKDAFDIWGQ
GTLVTVSS).

111.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain
variable region of the second arm comprises an amino acid sequence that is at least 90%
identical to SEQ ID NO: 56

(QVQLVQSGAEVKKPGSSVKV SCKASGGTFSSYAINWVRQAPGQGLEWMGGHIPIVA
TANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARRKGELKDAFDIWGQ
GTLVTVSS).

112.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain
variable region of the second arm comprises an amino acid sequence that is at least 90%
identical to SEQ ID NO: 57

(QVQLVQSGAEVKKPGSSVKV SCKASGGTFSSYAINWVRQAPGQGLEWMGGHIPIFG
KATYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARRKGELKDAFDIWGQ
GTLVTVSS).

113.—The multispecific antigen-binding construct of claim 93, wherein the heavy chain
variable region of the second arm comprises an amino acid sequence that is at least 90%
identical to SEQ ID NO: 58

(QVQLVQSGAEVKKPGSSVKV SCKASGGPFRSHAVSWVRQAPGQGLEWMGGHIPVF
GTATYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARLKSELKDAFDIWGQ
GTLVTVSS).

114.—The multispecific antigen-binding construct of claim 93, wherein the light chain
variable region of the second arm comprises an amino acid sequence that is at least 90%

identical to SEQ ID NO: 59

(DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK).

- 5 115.—The multispecific antigen-binding construct of claim 93, wherein the light chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 60

(DIQMTQSPSSLSASVGDRVTITCRASQWISSYLNWYQQKPGKAPKLLIYAASSLQSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK).

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- 116.—The multispecific antigen-binding construct of claim 93, wherein the light chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 61

(DIQMTQSPSSLSASVGDRVTITCRASQQISSYLNWYQQKPGKAPKLLIYAASSLQSG
15 VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK).

- 117.—The multispecific antigen-binding construct of claim 93, wherein the light chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 62

20 (DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISSLQPEDFATYYCFQSYSTPLTFGGGTKVEIK).

- 25 118.—The multispecific antigen-binding construct of claim 93, wherein the light chain variable region of the second arm comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 63

(DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTILTFGGGTKVEIK).

- 30 119.—The multispecific antigen-binding construct of any one of claims 1-118, wherein the construct is a bispecific antibody.

120.—The multispecific antigen-binding construct of claim 119, wherein the bispecific antibody is an antagonist of both PD-1 and PD-1 ligand.

~~1216.~~ The multispecific antigen-binding construct of ~~any one of claims 1-120,~~ wherein the first and the second antigen-binding arms each~~construct~~ comprises a common light chain variable region.

5 ~~122.—The multispecific antigen-binding construct of any one of claims 1-118, wherein one or both of the arms is an aptamer.~~

~~123.—The multispecific antigen-binding construct of any one of claims 1-118, wherein one or both of the arms is a protein other than an antibody.~~

10 ~~124.—The multispecific antigen-binding construct of any one of claims 1-121, wherein the construct comprises at least two bispecific antibodies.~~

15 ~~125.—The multispecific antigen-binding construct of claim 124, wherein one of the at least two bispecific antibodies is monovalent for PD-1.~~

~~126.—The multispecific antigen-binding construct of claim 124, wherein one of the at least two bispecific antibodies is monovalent for PD-1 ligand.~~

20 ~~127.—The multispecific antigen-binding construct of any one of claims 1-118, wherein at least one of the arms is a bivalent antibody specific for PD-1.~~

~~128.—The multispecific antigen-binding construct of any one of claims 1-118, wherein at least one of the arms is a bivalent antibody specific for PD-L1.~~

25 ~~129.—The multispecific antigen-binding construct of any one of claims 1-118, wherein at least one of the arms is a bivalent antibody specific for PD-1, and wherein at least one of the arms is a bivalent antibody specific for PD-L1.~~

30 ~~130.—The multispecific antigen-binding construct of claim 125, wherein the bispecific antibody binds two different epitopes on PD-1.~~

~~131.—The multispecific antigen-binding construct of claim 126, wherein the bispecific antibody binds two different epitopes on the PD-1 ligand.~~

~~132.—The multispecific antigen-binding construct of any one of claims 1-131, wherein the construct does not comprise an Fc domain.~~

~~133.—The multispecific antigen-binding construct of any one of claims 1-131, wherein the first arm or second arm, or both, comprises a heavy chain comprising one or more immunoglobulin Fc modifications.~~

~~134.—The multispecific antigen-binding construct of claim 133, wherein the immunoglobulin Fc domain of the heavy chain comprises one or more amino acid mutations that promote heterodimerization of the first and second arms.~~

~~135.—The multispecific antigen-binding construct of claim 134, wherein the mutation is present in a CH3 domain of the heavy chain.~~

~~136.—The multispecific antigen-binding construct of any one of claims 1-135, wherein the multispecific antigen-binding construct is produced in a quadroma cell.~~

~~137.—The multispecific antigen-binding construct of any one of claims 1-136, wherein the construct comprises one or more immunoglobulin constant region modifications.~~

~~138.—The multispecific antigen-binding construct of any one of claims 1-137, wherein the immunoglobulin constant region comprises one or more amino acid mutations that promote heterodimerization of antibodies.~~

~~139.—The multispecific antigen-binding construct of claim 138, wherein one or more mutations is present in the light chain constant region of one arm and one or more mutations is present in the heavy chain constant region of another arm.~~

~~140.—The multispecific antigen-binding construct of any one of claims 119 or 124-139, wherein the bispecific antibody is of a format selected from the group consisting of a bispecific IgG, bispecific antibody fragment, bispecific fusion protein, appended IgG, and bispecific antibody conjugate.~~

~~141.—The multispecific antigen-binding construct of any one of claims 133-140, wherein the Fc region has reduced effector function.~~

~~142.—The multispecific antigen-binding construct of any one of claims 133-141, wherein the Fc region enhances half-life of the construct.~~

~~143.—The multispecific antigen-binding construct of any one of claims 1-142, wherein at least one of the arms is bivalent for PD-1.~~

~~144.—The multispecific antigen-binding construct of any one of claims 1-142, wherein at least one of the arms is bivalent for PD-L1.~~

~~145.—The multispecific antigen-binding construct of any one of claims 1-142, wherein at least one of the arms is bivalent for PD-1, and at least one of the arms is bivalent for PD-L1.~~

~~146.—The multispecific antigen-binding construct of any one of claims 1-18, wherein the construct comprises a heavy chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 100 or 102.~~

~~147.—The multispecific antigen-binding construct of any one of claims 1-18, wherein the construct comprises a light chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 101 or 103.~~

~~148.—The multispecific antigen-binding construct of any one of claims 1-18, wherein the construct comprises a heavy chain amino acid sequence that is at least 85%, identical to the amino acid sequence of SEQ ID NO: 100, and wherein the construct comprises a light chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 101.~~

~~149.—The multispecific antigen-binding construct of any one of claims 1-18, wherein the construct comprises a heavy chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 102, and wherein the construct comprises a light chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 103.~~

~~150.—The multispecific antigen-binding construct of any one of claims 1-149, wherein binding of the multispecific antigen-binding construct causes a reduction of PD-1 expression by the immune cell.~~

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~~151.—The multispecific antigen-binding construct of any one of claims 1-150, wherein binding of the multispecific antigen-binding construct reduces PD-1 cell expression by inducing shedding of PD-1 from the immune cell.~~

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~~152.—A multispecific antigen-binding construct comprising at least two unit of antigen-binding, wherein a first unit of antigen-binding binds PD-1 and a second unit of antigen-binding binds a PD-1 ligand.~~

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~~153.—The multispecific antigen-binding construct of claim 152, wherein the first unit of antigen-binding binds PD-1 expressed by an immune cell.~~

~~154.—The multispecific antigen-binding construct of claims 152 or 153, wherein the second unit of antigen-binding binds a PD-1 ligand expressed by a second cell.~~

20

~~155.—The multispecific antigen-binding construct of any one of claims 152-154, wherein the multispecific antigen-binding construct blocks the interaction of PD-1 and the PD-1 ligand.~~

25

~~1567.~~ The multispecific antigen-binding construct of ~~any one of claims 152-1551~~, wherein the ~~multispecific antigen-binding~~ construct comprises at least two arms units of antigen-binding that bind PD-1 and at least two arms that bind PD-L1.

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8. The multispecific antigen-binding construct of claim 1, wherein the construct comprises a bivalent antibody specific for PD-1, and a bivalent antibody specific for PD-L1, wherein the bivalent antibody specific for PD-1 and the bivalent antibody specific for PD-L1 are linked.

9. The multispecific antigen-binding construct of claim 1, wherein the heavy chain of the first arm has an amino acid sequence that is at least 85% identical to the amino acid

sequence of SEQ ID NO: 100; and wherein the light chain of the first arm and the second arm has an amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 101.

5 10. The multispecific antigen-binding construct of claim 1, wherein heavy chain of the first arm has an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 100, and wherein the light chain of the first arm and the second arm have an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 101.

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11. The multispecific antigen-binding construct of claim 1, wherein the heavy chain of the first arm has an amino acid sequence of SEQ ID NO: 100, and wherein the light chain of the first arm and the second arm have an amino acid sequence of SEQ ID NO: 101.

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12. The multispecific antigen-binding construct of claim 1, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 90.

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13. The multispecific antigen-binding construct of claim 1, wherein the heavy chain variable region of the first arm comprises an amino acid sequence that is at least 99% identical to the amino acid sequence of SEQ ID NO: 90.

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14. The multispecific antigen-binding construct of claim 1, wherein the heavy chain variable region of the first arm comprises the amino acid sequence of SEQ ID NO: 90.

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15. The multispecific antigen-binding construct of claim 1, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 55.

16. The multispecific antigen-binding construct of claim 1, wherein the heavy chain variable region of the second arm comprises an amino acid sequence that is at least 99% identical to the amino acid sequence of SEQ ID NO: 55.

17. The multispecific antigen-binding construct of claim 1, wherein the heavy chain variable region of the second arm comprises the amino acid sequence of SEQ ID NO: 55.

18. The multispecific antigen-binding construct of claim 1, wherein the heavy chain of the first arm has an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 100, and wherein the light chain of the first arm and the second arm have an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 101.

19. The multispecific antigen-binding construct of claim 1, wherein the heavy chain of the first arm has an amino acid sequence that is at least 99% identical to the amino acid sequence of SEQ ID NO: 100, and wherein the light chain of the first arm and the second arm have an amino acid sequence that is at least 99% identical to the amino acid sequence of SEQ ID NO: 101.

20. The multispecific antigen-binding construct of claim 1, wherein the first arm binds PD-1 expressed by an immune cell.

21. The multispecific antigen-binding construct of claim 1, wherein the second arm binds a PD-1 ligand expressed by a second cell.

22. The multispecific antigen-binding construct of claim 21, wherein the second cell is a tumor cell and the PD-1 ligand is PD-L1.

~~157.—The multispecific antigen-binding construct of any one of claims 152-156, wherein the multispecific antigen-binding construct comprises at least two units of antigen-binding that bind a PD-1 ligand.~~

~~158.—The multispecific antigen-binding construct of any one of claims 152-157, wherein the multispecific antigen-binding construct comprises two units of antigen-binding that bind PD-1.~~

~~159.—The multispecific antigen-binding construct of any one of claims 152-158, wherein the multispecific antigen-binding construct comprises two units of antigen-binding that bind a PD-1 ligand.~~

5 ~~160.—The multispecific antigen-binding construct of any one of claims 152-159, wherein the multispecific antigen-binding construct comprises at least four units of antigen-binding, wherein two units of antigen-binding bind PD-1 and two units of antigen-binding bind a PD-1 ligand.~~

10 ~~161.—The multispecific antigen-binding construct of any one of claims 152-160, wherein the multispecific antigen-binding construct comprises four units of antigen-binding, wherein two units of antigen-binding bind PD-1 and two units of antigen-binding bind a PD-1 ligand.~~

15 ~~162.—The multispecific antigen-binding construct of of any one of claims 152-161, wherein binding of the multispecific antigen-binding construct causes a reduction of PD-1 expression by an immune cell.~~

20 ~~163.—The multispecific antigen-binding construct of any one of claims 152-162, wherein binding of the multispecific antigen-binding construct reduces PD-1 cell expression by inducing shedding of PD-1 from an immune cell.~~

~~164.—The multispecific antigen-binding construct of any one of claims 152-163, wherein the PD-1 ligand is PD-L2.~~

25 ~~165.—The multispecific antigen-binding construct of any one of claims 152-163, wherein the PD-1 ligand is PD-L1.~~

~~166.—The multispecific antigen-binding construct of claim 153, wherein the immune cell is a T cell.~~

30 ~~167.—The multispecific antigen-binding construct of claim 166, wherein the T cell is a CD8+ T cell.~~

168.—The multispecific antigen-binding construct of claim 153, wherein the immune cell is a natural killer (NK) cell.

169.—The multispecific antigen-binding construct of claim 153, wherein the immune cell is a macrophage.

170.—The multispecific antigen-binding construct of claim 154, wherein the second cell is a second immune cell.

171.—The multispecific antigen-binding construct of claim 170, wherein the second immune cell is any one or more of a T cell, a B cell, a macrophage, a myeloid-derived suppressor cell, a dendritic cell, or a mesenchymal stromal cell.

172.—The multispecific antigen-binding construct of claim 170, wherein the second immune cell is a regulatory T cell.

173.—The multispecific antigen-binding construct of claim 154, wherein the second cell is a tumor cell.

174.—The multispecific antigen-binding construct of claim 173, wherein the tumor cell is selected from the group consisting of a hematological cancer, a lymphoma, a myeloma, a leukemia, a neurological cancer, melanoma, breast cancer, a prostate cancer, a colorectal cancer, lung cancer, head and neck cancer, a gastrointestinal cancer, liver cancer, pancreatic cancer, a genitourinary cancer, a bone cancer, renal cancer, and a vascular cancer.

175.—The multispecific antigen-binding construct of any one of claims 152-174, wherein both units of antigen-binding have a K_D of at least 1×10^{-7} M, at least 1×10^{-8} M, at least 1×10^{-9} M, or at least 1×10^{-10} M.

176.—The multispecific antigen-binding construct of any one of claims 152-175, wherein the binding of one unit of antigen-binding to its target does not block the binding of the other unit of antigen-binding to its target.

177.—The multispecific antigen-binding construct of any one of claims 152-176, wherein the first unit of antigen-binding and second unit of antigen-binding bind to their respective targets and both unit of antigen-binding remain bound concurrently.

5 178.—The multispecific antigen-binding construct of any one of claims 152-177, wherein binding of the first unit of antigen-binding and the second unit of antigen-binding to their respective targets can bridge an immune cell and a second cell together.

10 179.—The multispecific antigen-binding construct of claim 178, wherein the bridging of the immune cell and the second cell is determined by flow cytometry.

180.—The multispecific antigen-binding construct of any one of claims 152-179, wherein the first unit of antigen-binding is an antagonist of PD-1.

15 181.—The multispecific antigen-binding construct of claim 180, wherein the first unit of antigen-binding comprises:

(a) a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 70 (FTFX₁X₂YAX₃X₄, wherein X₁=S, R, G, or N; X₂=D, S, N, A, R, or G; X₃=M or L; X₄=S, L, or N); (ii) a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYYTYA); and (iii) a CDRH3 comprising SEQ ID NO: 72 (ARGLDFIVGX₅TGNDY, wherein X₅=A, Y, or R); and
20 (b) a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

25 182.—The multispecific antigen-binding construct of claim 181, wherein:

(a) —CDRH1 of the first unit of antigen-binding comprises SEQ ID NO: 73 (FTFSDYAMS), CDRH2 of the first unit of antigen-binding comprises SEQ ID NO: 71 (SAISNSGTYYTYA), and CDRH3 of the first unit of antigen-binding comprises SEQ ID NO: 74 (ARGLDFIVGATGNDY);
30

(b) —CDRH1 of the first unit of antigen-binding comprises SEQ ID NO: 73 (FTFSDYAMS), CDRH2 of the first unit of antigen-binding comprises SEQ ID NO: 71 (SAISNSGTYYTYA), and CDRH3 of the first unit of antigen-binding comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY);

- (c) — CDRH1 of the first unit of antigen-binding comprises SEQ ID NO: 76 (FTFSSYAMS), CDRH2 of the first unit of antigen-binding comprises SEQ ID NO: 71 (SAISNSGTYYTYA), and CDRH3 of the first unit of antigen-binding comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY);
- 5 (d) — CDRH1 of the first unit of antigen-binding comprises SEQ ID NO: 77 (FTFSSYAML), CDRH2 of the first unit of antigen-binding comprises SEQ ID NO: 71 (SAISNSGTYYTYA), and CDRH3 of the first unit of antigen-binding comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY);
- 10 (e) — CDRH1 of the first unit of antigen-binding comprises SEQ ID NO: 78 (FTFSNYALS), CDRH2 of the first unit of antigen-binding comprises SEQ ID NO: 71 (SAISNSGTYYTYA), and CDRH3 of the first unit of antigen-binding comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY);
- 15 (f) — CDRH1 of the first unit of antigen-binding comprises SEQ ID NO: 79 (FTFSAYAMN), CDRH2 of the first unit of antigen-binding comprises SEQ ID NO: 71 (SAISNSGTYYTYA), and CDRH3 of the first unit of antigen-binding comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY);
- 20 (g) — CDRH1 of the first unit of antigen-binding comprises SEQ ID NO: 80 (FTFRSYAMS), CDRH2 of the first unit of antigen-binding comprises SEQ ID NO: 71 (SAISNSGTYYTYA), and CDRH3 of the first unit of antigen-binding comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY);
- 25 (h) — CDRH1 of the first unit of antigen-binding comprises SEQ ID NO: 81 (FTFGRYAMS), CDRH2 of the first unit of antigen-binding comprises SEQ ID NO: 71 (SAISNSGTYYTYA), and CDRH3 of the first unit of antigen-binding comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY);
- 30 (i) — CDRH1 of the first unit of antigen-binding comprises SEQ ID NO: 82 (FTFNSYAMS), CDRH2 of the first unit of antigen-binding comprises SEQ ID NO: 71 (SAISNSGTYYTYA), and CDRH3 of the first unit of antigen-binding comprises SEQ ID NO: 75 (ARGLDFIVGYTGNDY);
- (j) — CDRH1 of the first unit of antigen-binding comprises SEQ ID NO: 83 (FTFSNYAMS), CDRH2 of the first unit of antigen-binding comprises SEQ ID NO: 71 (SAISNSGTYYTYA), and CDRH3 of the first unit of antigen-binding comprises SEQ ID NO: 74 (ARGLDFIVGATGNDY);
- (k) — CDRH1 of the first unit of antigen-binding comprises SEQ ID NO: 84 (FTFSGYAMS), CDRH2 of the first unit of antigen-binding comprises SEQ ID NO: 71

(SAISNSGTYTYYA), and CDRH3 of the first unit of antigen-binding comprises SEQ ID NO: 85 (ARGLDFIVGRTGNDY);

(l) — CDRH1 of the first unit of antigen-binding comprises SEQ ID NO: 86 (FTFSSYAMN), CDRH2 of the first unit of antigen-binding comprises SEQ ID NO: 71 (SAISNSGTYTYYA) and CDRH3 of the first unit of antigen-binding comprises SEQ ID NO: 85 (ARGLDFIVGRTGNDY); or

(m) — CDRH1 of the first unit of antigen-binding comprises SEQ ID NO: 80 (FTFRSYAMS), CDRH2 of the first unit of antigen-binding comprises SEQ ID NO: 71 (SAISNSGTYTYYA), and CDRH3 of the first unit of antigen-binding comprises SEQ ID NO: 85 (ARGLDFIVGRTGNDY).

183. — The multispecific antigen-binding construct of claim 181, wherein:

(a) — the heavy chain variable region of the first unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 87;

(b) — the heavy chain variable region of the first unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 88;

(c) — the heavy chain variable region of the first unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 89;

(d) — the heavy chain variable region of the first unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 90;

(e) — the heavy chain variable region of the first unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 91;

(f) — the heavy chain variable region of the first unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 92;

(g) — the heavy chain variable region of the first unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 93;

(h) — the heavy chain variable region of the first unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 94;

(i) — the heavy chain variable region of the first unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 95;

(j) — the heavy chain variable region of the first unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 96;

(k) — the heavy chain variable region of the first unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 97;

(l) ~~the heavy chain variable region of the first unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 98; or~~
(m) ~~heavy chain variable region of the first unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 99.~~

184. ~~The multispecific antigen binding construct of any one of claims 181-183, wherein the light chain variable region of the first unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 59.~~

185. ~~The multispecific antigen binding construct of any one of claims 152-184, wherein the second unit of antigen binding is an antagonist of the PD-1 ligand.~~

186. ~~The multispecific antigen binding construct of any one of claims 152-185, wherein the second unit of antigen binding is an antagonist of PD-L2.~~

187. ~~The multispecific antigen binding construct of any one of claims 152-185, wherein the second unit of antigen binding is an antagonist of PD-L1.~~

188. ~~The multispecific antigen binding construct of claim 187, wherein the second unit of antigen binding comprises:~~

a. ~~a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN); (ii) a CDRH2 comprising SEQ ID NO: 2 (GGHPX₁X₂GX₃ATYA, wherein X₁ is V or I; X₂ is F, L, or V; and X₃ is T or A); and (iii) a CDRH3 comprising SEQ ID NO: 3 (ARLKX₁ELKDAFDI, wherein X₁ is G, F, or N); and~~
b. ~~a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 4 (RASQX₁ISSYLN, wherein X₁ is S, W, or Q); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 6 (X₁QSYSTPLT, wherein X₁ is Q or F).~~

189. ~~The multispecific antigen binding construct of claim 188, wherein:~~
(a) ~~CDRH1 of the second unit of antigen binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen binding comprises SEQ ID NO: 7 (GGHPILGAATYA), and CDRH3 of the second unit of antigen binding comprises SEQ ID NO: 8 (ARLKGELKDAFDI);~~

- (b) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 7 (GGHIPILGAATYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);
- (c) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHPVFGTATYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);
- (d) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHPVFGTATYA) and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGELKDAFDI);
- (e) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHPVFGTATYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 12 (RASQWISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);
- (f) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHPVFGTATYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 13 (RASQQISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);
- (g) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11

(GGHPVFGTATYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);

(h) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 15 (GGHIPFGIANYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGELKDAFDI);

(i) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 15 (GGHIPFGIANYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);

(j) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 16 (GGHPNFGTATYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 17 (ARLKGELKGAGDI);

(k) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 16 (GGHPNFGTATYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 17 (ARLKGELKGAGDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);

(l) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHPVFGTATYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 18 (ARLKFELKDAFDI);

(m) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHPVFGTATYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO:

~~18 (ARLKFEKDAFDI), CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);~~

5 (n) — ~~CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHPVFGTATYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 19 (ARLKGELKDAFDE);~~

10 (o) — ~~CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHPVFGTATYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 19 (ARLKGELKDAFDE), CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID~~
15 ~~NO: 10 (QQSYSTPLT);~~

(p) — ~~CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHPVFGTATYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 20 (ARLKNELKDAFDI);~~

20 (q) — ~~CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHPVFGTATYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 20 (ARLKNELKDAFDI), CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID~~
25 ~~NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);~~

(r) — ~~CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 21 (GGVIPFLGTANYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID~~
30 ~~NO: 22 (ARLKGILKDALDI);~~

(s) — ~~CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 21 (GGVIPFLGTANYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 22 (ARLKGILKDALDI), CDRL1 of the second unit of antigen-binding comprises SEQ~~

ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);

(t) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1

(GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 29 (GRHPIFGTADYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGELKDAFDI);

(u) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1

(GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 29 (GRHPIFGTADYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGELKDAFDI), CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);

(v) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1

(GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 31 (GGHIPILGTATYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 32 (ARRKGELKDAFDI);

(w) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1

(GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 31 (GGHIPILGTATYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 32 (ARRKGELKDAFDI), CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);

(x) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1

(GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 33 (GGHIPIVATANYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 32 (ARRKGELKDAFDI);

(y) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1

(GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 33 (GGHIPIVATANYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 32 (ARRKGELKDAFDI), CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID

NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);

(z) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 34 (GGHIPFGKATYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 32 (ARRKGELKDAFDI);

(aa) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 34 (GGHIPFGKATYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 32 (ARRKGELKDAFDI), CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);

(bb) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHIPVFGTATYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 38 (FQSYSTPLT);

(cc) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 1 (GTFSSYAIN), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHIPVFGTATYA), CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 39 (QQSYSTILT);

(dd) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 14 (GTFSSYAFS), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHIPVFGTATYA) and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGELKDAFDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);

(ee)——CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 23 (GTFSSYAIS), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 24 (GGHIPVGIANYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGEKDAFDI);

5 (ff)——CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 23 (GTFSSYAIS), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 24 (GGHIPVGIANYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGEKDAFDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);

10 (gg)——CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 23 (GTFSSYAIS), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHIPVFGTATYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 25 (ARLKGEFKDAFDI);

15 (hh)——CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 23 (GTFSSYAIS), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHIPVFGTATYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 25 (ARLKGEFKDAFDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);

20 (ii)——CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 23 (GTFSSYAIS), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 26 (GRIPLFGTAHYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGEKDAFDI);

25 (jj)——CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 23 (GTFSSYAIS), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 26 (GRIPLFGTAHYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 8 (ARLKGEKDAFDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);

(kk) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 23 (GTFSSYAIS), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 27 (GRINPILGTANYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 28 (ARLKGELKDAFSI);

5 (ll) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 23 (GTFSSYAIS), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 27 (GRINPILGTANYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 28 (ARLKGELKDAFSI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);

10 (mm) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 23 (GTFSSYAIS), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHPVFGTATYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 30 (ARLKGELKCAFDI);

15 (nn) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 23 (GTFSSYAIS), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHPVFGTATYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 30 (ARLKGELKCAFDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT);

20 (oo) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 36 (GPFRSHAVS), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHPVFGTATYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 37 (ARLKSELKDAFDI); or

25 (pp) — CDRH1 of the second unit of antigen-binding comprises SEQ ID NO: 36 (GPFRSHAVS), CDRH2 of the second unit of antigen-binding comprises SEQ ID NO: 11 (GGHPVFGTATYA), and CDRH3 of the second unit of antigen-binding comprises SEQ ID NO: 37 (ARLKSELKDAFDI); CDRL1 of the second unit of antigen-binding comprises SEQ ID NO: 9 (RASQSISSYLN); CDRL2 of the second unit of antigen-binding comprises SEQ ID NO: 5 (AASSLQS); and CDRL3 of the second unit of antigen-binding comprises SEQ ID NO: 10 (QQSYSTPLT).

190.—The multispecific antigen-binding construct of claim 188, wherein the second unit of antigen-binding comprises a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 35, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, or 58, and a light chain variable region comprising an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 59, 60, 61, 62, or 63.

191.—The multispecific antigen-binding construct of claim 188, wherein:

(a)—the heavy chain variable region of the second unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 35;

(b)—the heavy chain variable region of the second unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 40;

(c)—the heavy chain variable region of the second unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 41;

(d)—the heavy chain variable region of the second unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 42;

(e)—the heavy chain variable region of the second unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 43;

(f)—the heavy chain variable region of the second unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 44;

(g)—the heavy chain variable region of the second unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 45;

(h)—the heavy chain variable region of the second unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 46;

(i)—the heavy chain variable region of the second unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 47;

(j)—the heavy chain variable region of the second unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 48;

(k)—the heavy chain variable region of the second unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 49;

(l)—the heavy chain variable region of the second unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 50;

(m)—the heavy chain variable region of the second unit of antigen-binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 51;

(n) — the heavy chain variable region of the second unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 52;

(o) — the heavy chain variable region of the second unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 53;

5 (p) — the heavy chain variable region of the second unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 54;

(q) — the heavy chain variable region of the second unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 55;

10 (r) — the heavy chain variable region of the second unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 56;

(s) — the heavy chain variable region of the second unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 57; or

(t) — the heavy chain variable region of the second unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 58.

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192. — The multispecific antigen binding construct of claim 188, wherein:

(a) — the light chain variable region of the second unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 59;

20 (b) — the light chain variable region of the second unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 60;

(c) — the light chain variable region of the second unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 61;

(d) — the light chain variable region of the second unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 62; or

25 (e) — the light chain variable region of the second unit of antigen binding comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 63.

193. — The multispecific antigen binding construct of any one of claims 152-192, wherein the construct is a bispecific antibody.

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194. — The multispecific antigen binding construct of claim 193, wherein the bispecific antibody is an antagonist of both PD-1 and PD-1 ligand.

195.—The multispecific antigen-binding construct of any one of claims 152-194, wherein the construct comprises a common light chain.

196.—The multispecific antigen-binding construct of any one of claims 152-195, wherein the construct comprises at least two bivalent antibodies or antigen-binding portions thereof.

197.—The multispecific antigen-binding construct of any one of claims 152-196, wherein the construct comprises a bivalent antibody specific for PD-1.

198.—The multispecific antigen-binding construct of any one of claims 152-196, wherein the construct comprises a bivalent antibody specific for PD-L1.

199.—The multispecific antigen-binding construct of any one of claims 152-196, wherein the construct comprises a bivalent antibody specific for PD-1, and a bivalent antibody specific for PD-L1.

200.—The multispecific antigen-binding construct of claim 193, wherein the bispecific antibody binds two different epitopes on PD-1.

201.—The multispecific antigen-binding construct of claim 103, wherein the bispecific antibody binds two different epitopes on the PD-1 ligand.

202.—The multispecific antigen-binding construct of any one of claims 152-201, wherein the first unit of antigen-binding or second unit of antigen-binding, or both, comprises a heavy chain comprising one or more immunoglobulin Fc modifications.

203.—The multispecific antigen-binding construct of claim 202, wherein the immunoglobulin Fc domain of the heavy chain comprises one or more amino acid mutations that promote heterodimerization of the first and second units of antigen-binding.

204.—The multispecific antigen-binding construct of claim 203, wherein the mutation is present in a CH3 domain of the heavy chain.

205.—~~The multispecific antigen-binding construct of any one of claims 152-204, wherein the multispecific antigen-binding construct is produced in a quadroma cell.~~

206.—~~The multispecific antigen-binding construct of any one of claims 152-205, wherein the construct comprises one or more immunoglobulin constant region modifications.~~

207.—~~The multispecific antigen-binding construct of claim 206, wherein the immunoglobulin constant region comprises one or more amino acid mutations or substitutions that promote heterodimerization of antibodies.~~

208.—~~The multispecific antigen-binding construct of claim 207, wherein the one or more mutations is present in the light chain constant region of one unit of antigen-binding and the one or more mutations is present in the heavy chain constant region of another unit of antigen-binding.~~

209.—~~The multispecific antigen-binding construct of any one of claims 193-208, wherein the bispecific antibody is of a format selected from the group consisting of a bispecific IgG, bispecific antibody fragment, bispecific fusion protein, appended IgG, and bispecific antibody conjugate.~~

210.—~~The multispecific antigen-binding construct of any one of claims 152-209, wherein the construct comprises an Fc region having reduced effector function.~~

211.—~~The multispecific antigen-binding construct of any one of claims 152-210, wherein the construct comprises an Fc region that enhances half life of the construct.~~

212.—~~The multispecific antigen-binding construct of any one of claims 152-211, wherein the construct comprises a heavy chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 100 or 102.~~

213.—~~The multispecific antigen-binding construct of any one of claims 152-212, wherein the construct comprises a light chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 101 or 103.~~

214.—The multispecific antigen-binding construct of any one of claims 152-213, wherein the construct comprises a heavy chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 100, and wherein the construct comprises a light chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 101.

215.—The multispecific antigen-binding construct of any one of claims 152-213, wherein the construct comprises a heavy chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 102, and wherein the construct comprises a light chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 103.

216.—The multispecific antigen-binding construct of any one of claims 152-201, wherein the construct does not comprise an Fc domain.

217.—A multispecific antigen-binding construct comprising four units of antigen-binding, wherein a first and second unit of antigen-binding bind PD-1, and a third and fourth unit of antigen-binding bind PD-L1, wherein the multispecific antigen-binding construct blocks the interaction of PD-1 and PD-L1, and wherein the construct comprises a heavy chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 100, and a light chain amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 101.

218.—A nucleic acid encoding the multispecific antigen-binding construct according to any one of claims 1-217.

219.—An expression vector comprising the nucleic acid of claim 218.

220.—The expression vector of claim 219, further comprising one or more expression control sequences.

221.—A cell comprising the expression vector of claim 219 or 220.

222.—The cell of claim 221, wherein the cell is a mammalian cell.

223.—The cell of claim 222, wherein the mammalian cell is a rodent cell.

224.—The cell of claim 223, wherein the rodent cell is a CHO cell.

225.—A method for producing a multispecific antigen-binding construct, the method comprising culturing the cell of any one of claims 221-224 under conditions suitable for

expression of the multispecific antigen-binding construct from the expression vector by the cell.

226.—The method of claim 225, further comprising isolating the construct from the cell or media in which the cell is cultured.

227.—A pharmaceutical composition comprising the multispecific antigen-binding construct of any one of claims 1-217 and a pharmaceutically acceptable carrier.

228.—A protein-conjugate molecule comprising:

(a)—the multispecific antigen-binding construct of any one of claims 1-217 and

(b)—a heterologous moiety, wherein the heterologous moiety is conjugated to the multispecific antigen-binding construct of (a).

229.—The protein-conjugate molecule of claim 228, wherein the heterologous moiety is a therapeutic agent, a toxin, a drug, or a radioactive moiety.

230.—A method for treating a proliferative disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the multispecific antigen-binding construct according to any one of claims 1-217, or the pharmaceutical composition of claim 227 or the protein-conjugate molecule of claims 228 or 229, thereby treating the proliferative disorder in the subject.

231.—A method for treating or delaying progression of a cancer or reducing or inhibiting tumor growth in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the multispecific antigen-binding construct of any one of claims 1-217, or the pharmaceutical composition of claim 227 or the protein-conjugate molecule of claims 228 or 229, thereby treating or delaying progression of a cancer or reducing or inhibiting tumor growth in the subject.

232.—The method of claim 230, wherein the proliferative disorder is cancer.

233.—The method of claims 231 or 232, wherein the cancer is selected from the group consisting of a hematological cancer, a neurological cancer, melanoma, breast cancer, lung cancer, head and neck cancer, a gastrointestinal cancer, liver cancer, pancreatic cancer, a genitourinary cancer, a bone cancer, and a vascular cancer.

234.—The method of any one of claims 231-233, wherein the subject has a cancer that expresses PD-L1.

235.—A method of enhancing an immune response in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a multispecific antigen-binding construct according to any one of claims 1-217, or the pharmaceutical composition of claim 227 or the protein-conjugate molecule of claims 228 or 229, thereby enhancing the immune response in the subject.

236.—The method of claim 235, wherein the enhanced immune response comprises any one or more of enhanced T cell function, enhanced NK cell function, or enhanced macrophage function.

237.—The method of claim 236, wherein the enhancement of T cell function is greater upon administration of the multispecific antigen-binding construct as compared to an agent that binds either PD-1 or a PD-1 ligand, or a cocktail comprising an agent that binds PD-1 and an agent that binds a PD-1 ligand.

238.—The method of claim 237, wherein the T cell function is any one or more of increased IFN- γ production from T cells, enhanced T cell survival, increased T cell proliferation, or rescue from an exhausted T cell phenotype.

239.—The method of claim 238, wherein the enhanced T cell function is greater upon administration of the multispecific antigen-binding construct as compared to an agent that binds either PD-1 or a PD-1 ligand, or a cocktail comprising an agent that binds PD-1 and an agent that binds a PD-1 ligand.

240.—A method for enhancing an immune response against a cancer cell in a subject, the method comprising administering to the subject an effective amount of the multispecific antigen-binding constructs of any one of claims 1-217, or the pharmaceutical composition of claim 227 or the protein-conjugate molecule of claims 228 or 229, thereby enhancing an immune response against a cancer cell in the subject.

241.—The method of claim 240, wherein the enhanced immune response comprises any one or more of enhanced T cell function, enhanced NK cell function, or enhanced macrophage function.

242.—The method of claims 240 or 241, wherein the cancer cell is a hematological cancer cell, a lymphoma cell, a myeloma cell, a leukemia cell, a neurological cancer cell, a breast cancer cell, a prostate cancer cell, a skin cancer cell, a lung cancer cell, a bladder cancer cell, a kidney cancer cell, a head and neck cancer cell, a gastrointestinal cancer cell, a colorectal cancer cell, a liver cancer cell, a pancreatic cancer cell, a genitourinary cancer cell, a bone cancer cell, and a vascular cancer cell.

243.—The method of any one of claims 240–242, wherein the cancer cell expresses PD-L1.

244.—The method of any one of claims 240–243, wherein the multispecific antigen-binding construct or pharmaceutical composition or protein-conjugate molecule is administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, intramuscularly or intracranially.

245.—The method of any one of claims 230–244, further comprising administering an anti-cancer therapy to the subject.

246.—The method of claim 245, wherein the anti-cancer therapy is chemotherapy, immunotherapy, hormone therapy, cell therapy, cytokine therapy, radiotherapy, cryotherapy, or surgical therapy.

247.—The method of claims 245 or 246, wherein the anti-cancer therapy is administered prior to, concurrently with, or after treatment with the multispecific antigen-binding construct or pharmaceutical composition.

248.—The method of any one of claims 245–247, wherein the anti-cancer therapy is an immunotherapy and wherein the cancer in the subject is refractory to the immunotherapy in the absence of treatment with the multispecific antigen-binding construct or pharmaceutical composition, or the protein-conjugate.

249.—The multispecific antigen-binding construct, the pharmaceutical composition, or the protein-conjugate molecule of any one of claims 1–217 and 227–229, for use in treating a proliferative disorder in a subject.

250.—The multispecific antigen-binding construct, the pharmaceutical composition, or the protein-conjugate molecule of any one of claims 1–217 and 227–229, for use in treating cancer in a subject.

251.—The multispecific antigen-binding construct, the pharmaceutical composition, or the protein-conjugate molecule of any one of claims 1–217 and 227–229, for use in treating or delaying progression of a cancer or reducing or inhibiting tumor growth in a subject in need thereof.

252.—~~The multispecific antigen-binding construct, the pharmaceutical composition, or the protein-conjugate molecule of any one of claims 1-217 and 227-229, for use in enhancing an immune response in a subject.~~

5 253.—~~The multispecific antigen-binding construct, the pharmaceutical composition, or the protein-conjugate molecule of any one of claims 1-217 and 227-229, for use in enhancing an immune response against a cancer cell in a subject.~~

254.—~~The use of claim 249, wherein the proliferative disorder is cancer.~~

10 255.—~~The use of any one of claims 250, 251, 253, and 254 wherein the cancer is selected from the group consisting of a hematological cancer, a neurological cancer, melanoma, breast cancer, lung cancer, head and neck cancer, a gastrointestinal cancer, liver cancer, pancreatic cancer, a genitourinary cancer, a bone cancer, and a vascular cancer.~~

15 256.—~~The use of any one of claims 249-255, wherein the subject has a cancer that expresses PD-L1.~~

20 257.—~~The use of claims 252 or 253, wherein the enhanced immune response comprises any one or more of enhanced T cell function, enhanced NK cell function, or enhanced macrophage function.~~

25 258.—~~The use of claim 257, wherein the enhancement of T cell function is greater upon administration of the multispecific antigen-binding construct as compared to an agent that binds either PD-1 or a PD-1 ligand, or a cocktail comprising an agent that binds PD-1 and an agent that binds a PD-1 ligand.~~

30 259.—~~The use of claim 257, wherein the enhanced T cell function is any one or more of increased IFN- γ production from T cells, enhanced T cell survival, increased T cell proliferation, or rescue from an exhausted T cell phenotype.~~

260.—~~The use of any one of claims 249-259, wherein the multispecific antigen-binding construct or pharmaceutical composition or protein-conjugate molecule is administered~~

subcutaneously, intravenously, intradermally, intraperitoneally, orally, intramuscularly or intracranially.

261.—The use of any one of claims 249-260, wherein the use further comprises an anti-cancer therapy to the subject.

262.—The use of claim 261, wherein the anti-cancer therapy is chemotherapy, immunotherapy, hormone therapy, cell therapy, cytokine therapy, radiotherapy, cryotherapy, or surgical therapy.

263.—The use of claims 261 or 262, wherein the anti-cancer therapy is administered prior to, concurrently with, or after treatment with the multispecific antigen-binding construct or pharmaceutical composition or protein-conjugate molecule.

264.—The use of any one of claims 261-263, wherein the anti-cancer therapy is an immunotherapy and wherein the cancer in the subject is refractory to the immunotherapy in the absence of treatment with the multispecific antigen-binding construct or pharmaceutical composition or the protein-conjugate molecule.

265.—An anti-PD-1 antibody or antigen-binding fragment thereof, wherein the anti-PD-1 antibody or antigen-binding fragment comprises:

(a) a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 70 (FTFX₁X₂YAX₃X₄, wherein X₁=S, R, G, or N; X₂=D, S, N, A, R, or G; X₃=M or L; X₄=S, L, or N); (ii) a CDRH2 comprising SEQ ID NO: 71 (SAISNSGTYTYYA); and (iii) a CDRH3 comprising SEQ ID NO: 72 (ARGLDFIVGX₅TCNDY, wherein X₅=A, Y, or R); and

(b) a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QQSYSTPLT).

266.—The anti-PD-1 antibody or antigen-binding fragment thereof of claim 265, wherein the anti-PD-1 antibody or antigen-binding fragment comprises:

(a) a heavy chain variable region comprising (i) a CDRH1 comprising the amino acid sequence of any one of SEQ ID NOs: 73, 76, 77, 78, 79, 80, 81, 82, 83, 84, or 86; (ii) a CDRH2 comprising the amino acid sequence of SEQ ID NO: 71; and (iii) a CDRH3 comprising the amino acid sequence of any one of SEQ ID NOs: 74, 75, or 85; and

(b) a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 9 (RASQSISSYLN); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 10 (QSYSTPLT).

5 267. — The anti-PD-1 antibody or antigen-binding fragment thereof of claim 265 or 266, wherein the heavy chain variable region comprises an amino acid sequence that is at least 85% identical to the amino acid sequence of any one of SEQ ID NOs: 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99.

10 268. — The anti-PD-1 antibody or antigen-binding fragment thereof of any one of claims 265-267, wherein the light chain variable region comprises an amino acid sequence that is at least 85% identical to the amino acid sequence of SEQ ID NO: 59.

15 269. — An anti-PD-L1 antibody or antigen-binding fragment thereof, wherein the anti-PD-L1 antibody or antigen-binding fragment comprises:

a. — a heavy chain variable region comprising (i) a CDRH1 comprising SEQ ID NO: 1 (GTFSSYAIN); (ii) a CDRH2 comprising SEQ ID NO: 2 (GGHPX₁X₂GX₃ATYA, wherein X₁ is V or I; X₂ is F, L, or V; and X₃ is T or A); and (iii) a CDRH3 comprising SEQ ID NO: 3 (ARLKX₁ELKDAFDI, wherein X₁ is G, F, or N); and

20 b. — a light chain variable region comprising: (i) a CDRL1 comprising SEQ ID NO: 4 (RASQX₁ISSYLN, wherein X₁ is S, W, or Q); (ii) a CDRL2 comprising SEQ ID NO: 5 (AASSLQS); and (iii) a CDRL3 comprising SEQ ID NO: 6 (X₁QSYSTPLT, wherein X₁ is Q or F).

25 270. — The anti-PD-L1 antibody or antigen-binding fragment thereof of claim 269, wherein the anti-PD-L1 antibody or antigen-binding fragment comprises:

(a) a heavy chain variable region comprising (i) a CDRH1 comprising the amino acid sequence of any one of SEQ ID NOs: 1, 14, 23 or 36; (ii) a CDRH2 comprising the amino acid sequence of any one of SEQ ID NOs: 11, 15, 16, 21, 24, 26, 27, 29, 31, 33, or 34; and

30 (iii) a CDRH3 comprising the amino acid sequence of any one of SEQ ID NOs: 8, 17, 18, 19, 20, 22, 25, 28, 30, 32, or 37; and (b) a light chain variable region comprising: (i) a CDRL1 comprising the amino acid sequence of any one of SEQ ID NOs: 9, 12, or 13; (ii) a CDRL2 comprising the amino acid sequence of SEQ ID NO: 5; and (iii) a CDRL3 comprising the amino acid sequence of any one of SEQ ID NOs: 10, 38 or 39.

271. ~~The anti-PD-L1 antibody or antigen-binding fragment thereof of claim 269 or 270, wherein the heavy chain variable region comprises an amino acid sequence that is at least 85% identical to the amino acid sequence of any one of SEQ ID NOs: 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 35.~~

272. ~~The anti-PD-L1 antibody or antigen-binding fragment thereof of any one of claims 269-271, wherein the light chain variable region comprises an amino acid sequence that is at least 85% identical to the amino acid sequence of any one of SEQ ID NOs: 59, 60, 61, 62, or 63.~~

273. ~~The method of any one of claims 230-248, wherein the multispecific antigen-binding construct binds to PD-1 and to PD-L1 expressed on the surface of the same cell in the subject.~~

274. ~~The method of any one of claims 230-248, wherein the multispecific antigen-binding construct binds to PD-1 expressed on the surface of a first cell in the subject, and wherein the multispecific antigen-binding construct binds to PD-L1 expressed on the surface of a second cell in the subject.~~