

CLAIMS

What is claimed is:

1. An isolated anti-PD-1 construct comprising a single-domain antibody (sdAb) moiety specifically recognizing PD-1, wherein the sdAb moiety comprises a CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 37-72, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 109-144, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 181-216, or a variant thereof comprising up to about 3 amino acid substitutions.
2. The isolated anti-PD-1 construct of claim 1, wherein the sdAb moiety comprises a CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 37-72; a CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 109-144; and a CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 181-216; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions.
3. The isolated anti-PD-1 construct of claim 1 or 2, wherein the sdAb moiety comprises any one of the following:
 - (1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 37, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 109, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 181, or a variant thereof comprising up to about 3 amino acid substitutions;
 - (2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 110, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 182, or a variant thereof comprising up to about 3 amino acid substitutions;
 - (3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 111, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof comprising up to about 3 amino acid substitutions;
 - (4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 40, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID

- NO: 112, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 184, or a variant thereof comprising up to about 3 amino acid substitutions;
- (5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 41, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 113, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 185, or a variant thereof comprising up to about 3 amino acid substitutions;
- (6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 42, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 114, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 186, or a variant thereof comprising up to about 3 amino acid substitutions;
- (7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 43, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 115, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 187, or a variant thereof comprising up to about 3 amino acid substitutions;
- (8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 116, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 188, or a variant thereof comprising up to about 3 amino acid substitutions;
- (9) a CDR1 comprising the amino acid sequence of SEQ ID NO: 45, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 117, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189, or a variant thereof comprising up to about 3 amino acid substitutions;
- (10) a CDR1 comprising the amino acid sequence of SEQ ID NO: 46, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 118, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 190, or a variant thereof comprising up to about 3 amino acid substitutions;

- (11) a CDR1 comprising the amino acid sequence of SEQ ID NO: 47, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 119, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 191, or a variant thereof comprising up to about 3 amino acid substitutions;
- (12) a CDR1 comprising the amino acid sequence of SEQ ID NO: 48, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 120, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 192, or a variant thereof comprising up to about 3 amino acid substitutions;
- (13) a CDR1 comprising the amino acid sequence of SEQ ID NO: 49, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 121, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 193, or a variant thereof comprising up to about 3 amino acid substitutions;
- (14) a CDR1 comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 122, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 194, or a variant thereof comprising up to about 3 amino acid substitutions;
- (15) a CDR1 comprising the amino acid sequence of SEQ ID NO: 51, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 123, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 195, or a variant thereof comprising up to about 3 amino acid substitutions;
- (16) a CDR1 comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 124, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 196, or a variant thereof comprising up to about 3 amino acid substitutions;
- (17) a CDR1 comprising the amino acid sequence of SEQ ID NO: 53, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 125, or a variant thereof comprising up to about 3 amino acid substitutions; and a

- CDR3 comprising the amino acid sequence of SEQ ID NO: 197, or a variant thereof comprising up to about 3 amino acid substitutions;
- (18) a CDR1 comprising the amino acid sequence of SEQ ID NO: 54, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 126, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 198, or a variant thereof comprising up to about 3 amino acid substitutions;
- (19) a CDR1 comprising the amino acid sequence of SEQ ID NO: 55, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 127, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 199, or a variant thereof comprising up to about 3 amino acid substitutions;
- (20) a CDR1 comprising the amino acid sequence of SEQ ID NO: 56, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 128, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 200, or a variant thereof comprising up to about 3 amino acid substitutions;
- (21) a CDR1 comprising the amino acid sequence of SEQ ID NO: 57, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 129, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 201, or a variant thereof comprising up to about 3 amino acid substitutions;
- (22) a CDR1 comprising the amino acid sequence of SEQ ID NO: 58, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 130, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 202, or a variant thereof comprising up to about 3 amino acid substitutions;
- (23) a CDR1 comprising the amino acid sequence of SEQ ID NO: 59, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 131, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 203, or a variant thereof comprising up to about 3 amino acid substitutions;
- (24) a CDR1 comprising the amino acid sequence of SEQ ID NO: 60, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence

of SEQ ID NO: 132, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 204, or a variant thereof comprising up to about 3 amino acid substitutions;

- (25) a CDR1 comprising the amino acid sequence of SEQ ID NO: 61, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 133, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 205, or a variant thereof comprising up to about 3 amino acid substitutions;
- (26) a CDR1 comprising the amino acid sequence of SEQ ID NO: 62, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 134, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 206, or a variant thereof comprising up to about 3 amino acid substitutions;
- (27) a CDR1 comprising the amino acid sequence of SEQ ID NO: 63, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 135, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 207, or a variant thereof comprising up to about 3 amino acid substitutions;
- (28) a CDR1 comprising the amino acid sequence of SEQ ID NO: 64, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 136, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 208, or a variant thereof comprising up to about 3 amino acid substitutions;
- (29) a CDR1 comprising the amino acid sequence of SEQ ID NO: 65, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 137, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 209, or a variant thereof comprising up to about 3 amino acid substitutions;
- (30) a CDR1 comprising the amino acid sequence of SEQ ID NO: 66, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 138, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 210, or a variant thereof comprising up to about 3 amino acid substitutions;

- (31) a CDR1 comprising the amino acid sequence of SEQ ID NO: 67, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 139, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 211, or a variant thereof comprising up to about 3 amino acid substitutions;
 - (32) a CDR1 comprising the amino acid sequence of SEQ ID NO: 68, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 140, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 212, or a variant thereof comprising up to about 3 amino acid substitutions;
 - (33) a CDR1 comprising the amino acid sequence of SEQ ID NO: 69, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 141, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 213, or a variant thereof comprising up to about 3 amino acid substitutions;
 - (34) a CDR1 comprising the amino acid sequence of SEQ ID NO: 70, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 142, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 214, or a variant thereof comprising up to about 3 amino acid substitutions;
 - (35) a CDR1 comprising the amino acid sequence of SEQ ID NO: 71, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 143, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 215, or a variant thereof comprising up to about 3 amino acid substitutions; or
 - (36) a CDR1 comprising the amino acid sequence of SEQ ID NO: 72, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 144, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 216, or a variant thereof comprising up to about 3 amino acid substitutions.
4. The isolated anti-PD-1 construct of any one of claims 1-3, wherein the sdAb moiety comprises any one of the following:
- (1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 37; a CDR2 comprising the amino acid sequence of SEQ ID NO: 109; and a CDR3 comprising the amino acid sequence of SEQ ID

- NO: 181; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 38; a CDR2 comprising the amino acid sequence of SEQ ID NO: 110; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 182; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39; a CDR2 comprising the amino acid sequence of SEQ ID NO: 111; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 183; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 40; a CDR2 comprising the amino acid sequence of SEQ ID NO: 112; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 184; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 41; a CDR2 comprising the amino acid sequence of SEQ ID NO: 113; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 185; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 42; a CDR2 comprising the amino acid sequence of SEQ ID NO: 114; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 186; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 43; a CDR2 comprising the amino acid sequence of SEQ ID NO: 115; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 187; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 44; a CDR2 comprising the amino acid sequence of SEQ ID NO: 116; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 188; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (9) a CDR1 comprising the amino acid sequence of SEQ ID NO: 45; a CDR2 comprising the amino acid sequence of SEQ ID NO: 117; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;

- (10) a CDR1 comprising the amino acid sequence of SEQ ID NO: 46; a CDR2 comprising the amino acid sequence of SEQ ID NO: 118; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 190; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (11) a CDR1 comprising the amino acid sequence of SEQ ID NO: 47; a CDR2 comprising the amino acid sequence of SEQ ID NO: 119; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 191; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (12) a CDR1 comprising the amino acid sequence of SEQ ID NO: 48; a CDR2 comprising the amino acid sequence of SEQ ID NO: 120; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 192; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (13) a CDR1 comprising the amino acid sequence of SEQ ID NO: 49; a CDR2 comprising the amino acid sequence of SEQ ID NO: 121; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 193; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (14) a CDR1 comprising the amino acid sequence of SEQ ID NO: 50; a CDR2 comprising the amino acid sequence of SEQ ID NO: 122; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 194; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (15) a CDR1 comprising the amino acid sequence of SEQ ID NO: 51; a CDR2 comprising the amino acid sequence of SEQ ID NO: 123; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 195; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (16) a CDR1 comprising the amino acid sequence of SEQ ID NO: 52; a CDR2 comprising the amino acid sequence of SEQ ID NO: 124; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 196; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (17) a CDR1 comprising the amino acid sequence of SEQ ID NO: 53; a CDR2 comprising the amino acid sequence of SEQ ID NO: 125; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 197; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (18) a CDR1 comprising the amino acid sequence of SEQ ID NO: 54; a CDR2 comprising the amino acid sequence of SEQ ID NO: 126; and a CDR3 comprising the amino acid sequence of

SEQ ID NO: 198; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;

- (19) a CDR1 comprising the amino acid sequence of SEQ ID NO: 55; a CDR2 comprising the amino acid sequence of SEQ ID NO: 127; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 199; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (20) a CDR1 comprising the amino acid sequence of SEQ ID NO: 56; a CDR2 comprising the amino acid sequence of SEQ ID NO: 128; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 200; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (21) a CDR1 comprising the amino acid sequence of SEQ ID NO: 57; a CDR2 comprising the amino acid sequence of SEQ ID NO: 129; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 201; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (22) a CDR1 comprising the amino acid sequence of SEQ ID NO: 58; a CDR2 comprising the amino acid sequence of SEQ ID NO: 130; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 202; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (23) a CDR1 comprising the amino acid sequence of SEQ ID NO: 59; a CDR2 comprising the amino acid sequence of SEQ ID NO: 131; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 203; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (24) a CDR1 comprising the amino acid sequence of SEQ ID NO: 60; a CDR2 comprising the amino acid sequence of SEQ ID NO: 132; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 204; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (25) a CDR1 comprising the amino acid sequence of SEQ ID NO: 61; a CDR2 comprising the amino acid sequence of SEQ ID NO: 133; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 205; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (26) a CDR1 comprising the amino acid sequence of SEQ ID NO: 62; a CDR2 comprising the amino acid sequence of SEQ ID NO: 134; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 206; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;

- (27) a CDR1 comprising the amino acid sequence of SEQ ID NO: 63; a CDR2 comprising the amino acid sequence of SEQ ID NO: 135; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 207; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (28) a CDR1 comprising the amino acid sequence of SEQ ID NO: 64; a CDR2 comprising the amino acid sequence of SEQ ID NO: 136; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 208; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (29) a CDR1 comprising the amino acid sequence of SEQ ID NO: 65; a CDR2 comprising the amino acid sequence of SEQ ID NO: 137; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 209; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (30) a CDR1 comprising the amino acid sequence of SEQ ID NO: 66; a CDR2 comprising the amino acid sequence of SEQ ID NO: 138; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 210; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (31) a CDR1 comprising the amino acid sequence of SEQ ID NO: 67; a CDR2 comprising the amino acid sequence of SEQ ID NO: 139; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 211; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (32) a CDR1 comprising the amino acid sequence of SEQ ID NO: 68; a CDR2 comprising the amino acid sequence of SEQ ID NO: 140; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 212; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (33) a CDR1 comprising the amino acid sequence of SEQ ID NO: 69; a CDR2 comprising the amino acid sequence of SEQ ID NO: 141; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 213; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (34) a CDR1 comprising the amino acid sequence of SEQ ID NO: 70; a CDR2 comprising the amino acid sequence of SEQ ID NO: 142; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 214; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions;
- (35) a CDR1 comprising the amino acid sequence of SEQ ID NO: 71; a CDR2 comprising the amino acid sequence of SEQ ID NO: 143; and a CDR3 comprising the amino acid sequence of

- SEQ ID NO: 215; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions; or
- (36) a CDR1 comprising the amino acid sequence of SEQ ID NO: 72; a CDR2 comprising the amino acid sequence of SEQ ID NO: 144; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 216; or a variant thereof comprising up to about 3 amino acid substitutions in the CDR regions.
5. The isolated anti-PD-1 construct of any one of claims 1-4, wherein the sdAb moiety comprises a V_HH domain comprising the amino acid sequence of any one of the following:
 - a-1) the amino acid residue at position 37 is selected from the group consisting of F, Y, L, I, and V;
 - a-2) the amino acid residue at position 44 is selected from the group consisting of A, G, E, D, G, Q, R, S, and L;
 - a-3) the amino acid residue at position 45 is selected from the group consisting of L, R, and C;
 - a-4) the amino acid residue at position 103 is selected from the group consisting of W, R, G, and S;
 - and
 - a-5) the amino acid residue at position 108 is Q; or
 - b-1) the amino acid residue at position 37 is selected from the group consisting of F, Y, L, I, and V;
 - b-2) the amino acid residue at position 44 is selected from the group consisting of E, Q, and G;
 - b-3) the amino acid residue at position 45 is R;
 - b-4) the amino acid residue at position 103 is selected from the group consisting of W, R, and S; and
 - b-5) the amino acid residue at position 108 is selected from the group consisting of Q and L;
 wherein the amino acid position is according to Kabat numbering, and wherein position 108 can be optionally humanized to L when position 108 is Q.
 6. The isolated anti-PD-1 construct of any one of claims 1-5, wherein the sdAb moiety comprises a V_HH domain comprising the amino acid sequence of any one of SEQ ID NOs: 289-324, or a variant thereof having at least about 80% sequence identity to any one of SEQ ID NOs: 289-324.
 7. The isolated anti-PD-1 construct of claim 6, wherein the sdAb moiety comprises a V_HH domain comprising the amino acid sequence of any one of SEQ ID NOs: 289-324, or a variant thereof comprising up to about 3 amino acid substitutions in the V_HH domain.
 8. The isolated anti-PD-1 construct of any one of claims 1-7, wherein the K_d of the binding between the sdAb moiety and PD-1 is about 10⁻⁵ M to about 10⁻¹² M.
 9. The isolated anti-PD-1 construct of claim 8, wherein the K_d of the binding between the sdAb moiety and PD-1 is about 10⁻⁷ M to about 10⁻¹² M.
 10. The isolated anti-PD-1 construct of any one of claims 1-9, wherein the sdAb moiety specifically recognizing PD-1 is camelid, chimeric, human, partially humanized, or fully humanized.

11. The isolated anti-PD-1 construct of any one of claims 1-10, wherein the isolated anti-PD-1 construct is a heavy chain-only antibody (HCAb) comprising the sdAb moiety specifically recognizing PD-1 fused to an Fc fragment via an optional linker.
12. The isolated anti-PD-1 construct of claim 11, wherein the HCAb is monomeric or dimeric.
13. The isolated anti-PD-1 construct of claim 11 or 12, wherein the Fc fragment is a human IgG1 (hIgG1) Fc, effectorless (inert) hIgG1 Fc, hIgG4 Fc, or hIgG4 Fc (S228P).
14. The isolated anti-PD-1 construct of any one of claims 11-13, wherein the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 367-376.
15. The isolated anti-PD-1 construct of any one of claims 11-14, wherein the HCAb comprises the amino acid sequence of any one of SEQ ID NOs: 325-360.
16. The isolated anti-PD-1 construct of any one of claims 1-10, wherein the isolated anti-PD-1 construct further comprises a second antibody moiety specifically recognizing a second epitope.
17. The isolated anti-PD-1 construct of claim 16, wherein the second antibody moiety is a full-length antibody, a Fab, a Fab', a (Fab')₂, an Fv, a single chain Fv (scFv), an scFv-scFv, a minibody, a diabody, or an sdAb.
18. The isolated anti-PD-1 construct of claim 16 or 17, wherein the anti-PD-1 construct is multispecific.
19. The isolated anti-PD-1 construct of any one of claims 16-18, wherein the sdAb moiety specifically recognizing PD-1 and the second antibody moiety are optionally connected by a peptide linker.
20. The isolated anti-PD-1 construct of claim 19, wherein the peptide linker comprises the amino acid sequence of any one of SEQ ID NOs: 367-376.
21. The isolated anti-PD-1 construct of any one of claims 16-20, wherein the second antibody moiety is a second sdAb specifically recognizing PD-1 or CTLA-4.
22. The isolated anti-PD-1 construct of any one of claims 16-20, wherein the second antibody moiety is a full-length antibody consisting of two heavy chains and two light chains.
23. The isolated anti-PD-1 construct of claim 22, wherein the Fc fragment of the heavy chain is human IgG1 (hIgG1) Fc, effectorless (inert) hIgG1 Fc, hIgG4 Fc, or hIgG4 Fc (S228P).
24. The isolated anti-PD-1 construct of claim 22 or 23, wherein the N-terminus of the sdAb moiety specifically recognizing PD-1 is fused to the C-terminus of at least one of the heavy chains of the full-length antibody.
25. The isolated anti-PD-1 construct of claim 22 or 23, wherein the C-terminus of the sdAb moiety specifically recognizing PD-1 is fused to the N-terminus of at least one of the heavy chains of the full-length antibody.

26. The isolated anti-PD-1 construct of claim 22 or 23, wherein the N-terminus of the sdAb moiety specifically recognizing PD-1 is fused to the C-terminus of at least one of the light chains of the full-length antibody.
27. The isolated anti-PD-1 construct of claim 22 or 23, wherein the C-terminus of the sdAb moiety specifically recognizing PD-1 is fused to the N-terminus of at least one of the light chains of the full-length antibody.
28. The isolated anti-PD-1 construct of any one of claims 22-27, wherein the full-length antibody specifically recognizes TIGIT.
29. The isolated anti-PD-1 construct of claim 28, wherein the full-length antibody comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a heavy chain comprising the amino acid sequence of SEQ ID NO: 377, and LC-CDR1, LC-CDR2, and LC-CDR3 of a light chain comprising the amino acid sequence of SEQ ID NO: 378.
30. The isolated anti-PD-1 construct of claim 28 or 29, wherein the full-length antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 377, and a light chain comprising the amino acid sequence of SEQ ID NO: 378.
31. The isolated anti-PD-1 construct of any one of claims 22-27, wherein the full-length antibody specifically recognizes LAG-3.
32. The isolated anti-PD-1 construct of claim 31, wherein the full-length antibody comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a heavy chain comprising the amino acid sequence of SEQ ID NO: 379, and LC-CDR1, LC-CDR2, and LC-CDR3 of a light chain comprising the amino acid sequence of SEQ ID NO: 380.
33. The isolated anti-PD-1 construct of claim 31 or 32, wherein the full-length antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 379, and a light chain comprising the amino acid sequence of SEQ ID NO: 380.
34. The isolated anti-PD-1 construct of any one of claims 22-27, wherein the full-length antibody specifically recognizes TIM-3.
35. The isolated anti-PD-1 construct of claim 34, wherein the full-length antibody comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a heavy chain comprising the amino acid sequence of SEQ ID NO: 381, and LC-CDR1, LC-CDR2, and LC-CDR3 of a light chain comprising the amino acid sequence of SEQ ID NO: 382.
36. The isolated anti-PD-1 construct of claim 34 or 35, wherein the full-length antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 381, and a light chain comprising the amino acid sequence of SEQ ID NO: 382.

37. The isolated anti-PD-1 construct of any one of claims 22-27, wherein the full-length antibody specifically recognizes CTLA-4.
38. The isolated anti-PD-1 construct of claim 37, wherein the full-length antibody comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a heavy chain comprising the amino acid sequence of SEQ ID NO: 383, and LC-CDR1, LC-CDR2, and LC-CDR3 of a light chain comprising the amino acid sequence of SEQ ID NO: 384.
39. The isolated anti-PD-1 construct of claim 37 or 38, wherein the full-length antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 383, and a light chain comprising the amino acid sequence of SEQ ID NO: 384.
40. The isolated anti-PD-1 construct of any one of claims 22-27, wherein the full-length antibody specifically recognizes PD-1.
41. The isolated anti-PD-1 construct of claim 40, wherein the full-length antibody comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a heavy chain comprising the amino acid sequence of SEQ ID NO: 385, and LC-CDR1, LC-CDR2, and LC-CDR3 of a light chain comprising the amino acid sequence of SEQ ID NO: 386.
42. The isolated anti-PD-1 construct of claim 40 or 41, wherein the full-length antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 385, and a light chain comprising the amino acid sequence of SEQ ID NO: 386.
43. An isolated anti-PD-1 construct comprising an sdAb moiety specifically recognizing PD-1, wherein the sdAb moiety comprises CDR1, CDR2, and CDR3 of any one of SEQ ID NOs: 289-324.
44. An isolated anti-PD-1 construct that specifically binds to PD-1 competitively with the isolated anti-PD-1 construct of any one of claims 1-43.
45. A pharmaceutical composition comprising the isolated anti-PD-1 construct of any one of claims 1-44, and optionally a pharmaceutical acceptable carrier.
46. A method of treating an individual having a PD-1-related disease, comprising administering to the individual an effective amount of the pharmaceutical composition of claim 45.
47. The method of claim 46, wherein the PD-1-related disease is cancer.
48. The method of claim 47, wherein the cancer is a solid tumor.
49. The method of claim 48, wherein the cancer is a colon cancer.
50. The method of any one of claims 46-49, further comprising administering to the individual an additional therapy.
51. The method of any one of claims 46-50, wherein the individual is a human.
52. An isolated nucleic acid encoding the isolated anti-PD-1 construct of any one of claims 1-44.
53. A vector comprising the isolated nucleic acid of claim 52.

54. An isolated host cell comprising the isolated nucleic acid of claim 52, or the vector of claim 53.
55. A kit comprising the isolated anti-PD-1 construct of any one of claims 1-44, the isolated nucleic acid of claim 52, the vector of claim 53, or the isolated host cell of claim 54.
56. A method of producing an anti-PD-1 construct, comprising: (a) culturing a host cell comprising the isolated nucleic acid of claim 52 or the vector of claim 53, or the isolated host cell of claim 54 under conditions effective to express the encoded anti-PD-1 construct; and (b) obtaining the expressed anti-PD-1 construct from said host cell.
57. The method of claim 56, wherein step (a) further comprises producing a host cell comprising the isolated nucleic acid of claim 52 or the vector of claim 53.