

[0015] However, despite all such prior advances, a need remains for improved compositions capable of more vigorously directing the body's immune system to attack cancer cells or pathogen-infected cells, especially at lower therapeutic concentrations. For although the adaptive immune system can be a potent defense mechanism against cancer and disease, it is often hampered by immune suppressive mechanisms in the tumor microenvironment, such as the expression of PD-1. Furthermore, co-inhibitory molecules expressed by tumor cells, immune cells, and stromal cells in the tumor milieu can dominantly attenuate T-cell responses against cancer cells. Thus, a need remains for potent PD-1-binding molecules. In particular, a need exists for potent PD-1-binding molecules having a desirable binding kinetic profile and that antagonize the PD-1/PD-L1 axis by blocking the PD-1/PD-L1 interaction, which could provide improved therapeutic value to patients suffering from cancer or other diseases and conditions. The present invention is directed to these and other goals.

Summary

[0016] The present disclosure is directed to PD-1 binding molecules that comprise the PD-1-binding domain of selected anti-PD-1 antibodies capable of binding to both cynomolgus monkey PD-1 and to human PD-1: PD-1 mAb 1, PD-1 mAb 2, PD-1 mAb 3, PD-1 mAb 4, PD-1 mAb 5, PD-1 mAb 6, PD-1 mAb 7, PD-1 mAb 8, PD-1 mAb 9, PD-1 mAb 10, PD-1 mAb 11, PD-1 mAb 12, PD-1 mAb 13, PD-1 mAb 14, or PD-1 mAb 15. The disclosure particularly concerns PD-1 binding molecules that are humanized or chimeric versions of such antibodies, or that comprise PD-1 binding-fragments of such anti-PD-1 antibodies (especially immunoconjugates, diabodies, BiTEs, bispecific antibodies, *etc.*). The disclosure particularly concerns such PD-1-binding molecules that are additionally capable of binding an epitope of a molecule involved in regulating an immune check point that is present on the surface of an immune cell. The present disclosure also pertains to methods of using such PD-1-binding molecules to detect PD-1 or to stimulate an immune response. The present disclosure also pertains to methods of combination therapy in which a PD-1-binding molecule that comprises one or more PD-1-binding domain(s) of such selected anti-PD-1 antibodies is administered in combination with one or more additional molecules that are effective in stimulating an immune response and/or in combination with one or more additional molecules that specifically bind a cancer antigen.

[0017] In detail, the disclosure provides an anti-human PD-1-binding molecule that comprises the three Heavy Chain CDR Domains, CDR_H1, CDR_H2 and CDR_H3 and the three Light Chain CDR Domains, CDR_L1, CDR_L2, and CDR_L3, wherein:

- (A) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:76**, **SEQ ID NO:77**, and **SEQ ID NO:78**;

or

- (B) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:85**, **SEQ ID NO:86**, and **SEQ ID NO:87**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 2, and, respectively have the amino acid sequences: **SEQ ID NO:90**, **SEQ ID NO:91**, and **SEQ ID NO:92**;

or

- (C) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 3, and respectively have the amino acid sequences: **SEQ ID NO:99**, **SEQ ID NO:100**, and **SEQ ID NO:101**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 3, and, respectively have the amino acid sequences: **SEQ ID NO:104**, **SEQ ID NO:105**, and **SEQ ID NO:106**;

or

- (D) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 4, and respectively have the amino acid sequences: **SEQ ID NO:109**, **SEQ ID NO:110**, and **SEQ ID NO:111**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 4, and, respectively have the amino acid sequences: **SEQ ID NO:114**, **SEQ ID NO:115**, and **SEQ ID NO:116**;

amino acid sequences: **SEQ ID NO:139**, **SEQ ID NO:140**, and **SEQ ID NO:141**; and

- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of hPD-1 mAb 7(1.3), and, respectively have the amino acid sequences: **SEQ ID NO:157**, **SEQ ID NO:158**, and **SEQ ID NO:145**;

or

- (R) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of hPD-1 mAb 9(2.2), and respectively have the amino acid sequences: **SEQ ID NO:183**, **SEQ ID NO:172**, and **SEQ ID NO:173**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of hPD-1 mAb 9(2.2), and, respectively have the amino acid sequences: **SEQ ID NO:188**, **SEQ ID NO:189**, and **SEQ ID NO:178**.

[0017a] In a first aspect, there is provided an anti-human PD-1-binding monospecific monoclonal antibody that comprises a Variable Heavy Chain Domain and a Variable Light Chain Domain, wherein:

said Variable Heavy Chain Domain comprises a CDR_{H1} Domain, a CDR_{H2} Domain and a CDR_{H3} Domain, and said Variable Light Chain Domain comprises a CDR_{L1} Domain, a CDR_{L2} Domain, and a CDR_{L3} Domain, wherein:

- (A) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of PD-1 mAb 5, and respectively comprise the amino acid sequences: **SEQ ID NO:119**, **SEQ ID NO:120**, and **SEQ ID NO:121**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of PD-1 mAb 5, and, respectively comprise the amino acid sequences: **SEQ ID NO:124**, **SEQ ID NO:125**, and **SEQ ID NO:126**;

or

- (B) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of PD-1 mAb 7, and respectively comprise the amino acid sequences: **SEQ ID NO:139**, **SEQ ID NO:140**, and **SEQ ID NO:141**;
- and

- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 7, and, respectively comprise the amino acid sequences: **SEQ ID NO:144**, **SEQ ID NO:145**, and **SEQ ID NO:146**;
or
- (C) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of hPD-1 mAb 7(1.2), and respectively comprise the amino acid sequences: **SEQ ID NO:139**, **SEQ ID NO:140**, and **SEQ ID NO:141**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hPD-1 mAb 7(1.2), and, respectively comprise the amino acid sequences: **SEQ ID NO:157**, **SEQ ID NO:145**, and **SEQ ID NO:146**;
or
- (D) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of hPD-1 mAb 7(1.3), and respectively comprise the amino acid sequences: **SEQ ID NO:139**, **SEQ ID NO:140**, and **SEQ ID NO:141**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hPD-1 mAb 7(1.3), and, respectively comprise the amino acid sequences: **SEQ ID NO:157**, **SEQ ID NO:158**, and **SEQ ID NO:145**.

[0017b] In a second aspect, there is provided a composition comprising the anti-human PD-1-binding monospecific monoclonal antibody of the first aspect and a pharmaceutically acceptable carrier.

[0017c] In a third aspect, there is provided a multispecific anti-human PD-1-binding molecule that comprises a Variable Heavy Chain Domain and a Variable Light Chain Domain, wherein:

said Variable Heavy Chain Domain comprises a CDR_H1 Domain, a CDR_H2 Domain and a CDR_H3 Domain, and said Variable Light Chain Domain comprises a CDR_L1 Domain, a CDR_L2 Domain, and a CDR_L3 Domain, wherein:

- (A) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 1, and respectively comprise the

- amino acid sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of PD-1 mAb 1, and respectively comprise the amino acid sequences: **SEQ ID NO:76**, **SEQ ID NO:77**, and **SEQ ID NO:78**;
- or
- (B) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of PD-1 mAb 2, and respectively comprise the amino acid sequences: **SEQ ID NO:85**, **SEQ ID NO:86**, and **SEQ ID NO:87**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of PD-1 mAb 2, and, respectively comprise the amino acid sequences: **SEQ ID NO:90**, **SEQ ID NO:91**, and **SEQ ID NO:92**;
- or
- (C) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of PD-1 mAb 3, and respectively comprise the amino acid sequences: **SEQ ID NO:99**, **SEQ ID NO:100**, and **SEQ ID NO:101**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of PD-1 mAb 3, and, respectively comprise the amino acid sequences: **SEQ ID NO:104**, **SEQ ID NO:105**, and **SEQ ID NO:106**;
- or
- (D) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of PD-1 mAb 4, and respectively comprise the amino acid sequences: **SEQ ID NO:109**, **SEQ ID NO:110**, and **SEQ ID NO:111**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of PD-1 mAb 4, and, respectively comprise the amino acid sequences: **SEQ ID NO:114**, **SEQ ID NO:115**, and **SEQ ID NO:116**;
- or
- (E) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of PD-1 mAb 5, and respectively comprise the amino acid sequences: **SEQ ID NO:119**, **SEQ ID NO:120**, and **SEQ ID NO:121**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of PD-1 mAb 5, and, respectively comprise the amino acid sequences: **SEQ ID NO:124**, **SEQ ID NO:125**, and **SEQ ID NO:126**;
- or
- (F) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of PD-1 mAb 6, and respectively comprise the amino acid sequences: **SEQ ID NO:129**, **SEQ ID NO:130**, and **SEQ ID NO:131**; and

- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 6, and, respectively comprise the amino acid sequences: **SEQ ID NO:134**, **SEQ ID NO:135**, and **SEQ ID NO:136**;
or
- (G) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 7, and respectively comprise the amino acid sequences: **SEQ ID NO:139**, **SEQ ID NO:140**, and **SEQ ID NO:141**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 7, and, respectively comprise the amino acid sequences: **SEQ ID NO:144**, **SEQ ID NO:145**, and **SEQ ID NO:146**;
or
- (H) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 8, and respectively comprise the amino acid sequences: **SEQ ID NO:161**, **SEQ ID NO:162**, and **SEQ ID NO:163**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 8, and, respectively comprise the amino acid sequences: **SEQ ID NO:166**, **SEQ ID NO:167**, and **SEQ ID NO:168**;
or
- (I) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 9, and respectively comprise the amino acid sequences: **SEQ ID NO:171**, **SEQ ID NO:172**, and **SEQ ID NO:173**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 9, and, respectively comprise the amino acid sequences: **SEQ ID NO:176**, **SEQ ID NO:177**, and **SEQ ID NO:178**;
or
- (J) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 10, and respectively comprise the amino acid sequences: **SEQ ID NO:192**, **SEQ ID NO:193**, and **SEQ ID NO:194**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 10, and, respectively comprise the amino acid sequences: **SEQ ID NO:197**, **SEQ ID NO:198**, and **SEQ ID NO:199**;
or
- (K) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 11, and respectively comprise the amino acid sequences: **SEQ ID NO:202**, **SEQ ID NO:203**, and **SEQ ID NO:204**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 11, and, respectively comprise the amino

acid sequences: **SEQ ID NO:207**, **SEQ ID NO:208**, and **SEQ ID NO:209**;

or

(L) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of PD-1 mAb 12, and respectively comprise the amino acid sequences: **SEQ ID NO:212**, **SEQ ID NO:213**, and **SEQ ID NO:214**; and

(2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of PD-1 mAb 12, and, respectively comprise the amino acid sequences: **SEQ ID NO:217**, **SEQ ID NO:218**, and **SEQ ID NO:219**;

or

(M) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of PD-1 mAb 13, and respectively comprise the amino acid sequences: **SEQ ID NO:222**, **SEQ ID NO:223**, and **SEQ ID NO:224**; and

(2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of PD-1 mAb 13, and, respectively comprise the amino acid sequences: **SEQ ID NO:227**, **SEQ ID NO:228**, and **SEQ ID NO:229**;

or

(N) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of PD-1 mAb 14, and respectively comprise the amino acid sequences: **SEQ ID NO:232**, **SEQ ID NO:233**, and **SEQ ID NO:234**; and

(2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of PD-1 mAb 14, and, respectively comprise the amino acid sequences: **SEQ ID NO:237**, **SEQ ID NO:238**, and **SEQ ID NO:239**;

or

(O) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of PD-1 mAb 15, and respectively comprise the amino acid sequences: **SEQ ID NO:242**, **SEQ ID NO:243**, and **SEQ ID NO:244**; and

(2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of PD-1 mAb 15, and, respectively comprise the amino acid sequences: **SEQ ID NO:247**, **SEQ ID NO:248**, and **SEQ ID NO:249**;

or

(P) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of hPD-1 mAb 7(1.2), and respectively comprise the amino acid sequences: **SEQ ID NO:139**, **SEQ ID NO:140**, and **SEQ ID NO:141**; and

- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hPD-1 mAb 7(1.2), and, respectively comprise the amino acid sequences: **SEQ ID NO:157, SEQ ID NO:145, and SEQ ID NO:146;**
or
- (Q) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of hPD-1 mAb 7(1.3), and respectively comprise the amino acid sequences: **SEQ ID NO:139, SEQ ID NO:140, and SEQ ID NO:141;** and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hPD-1 mAb 7(1.3), and, respectively comprise the amino acid sequences: **SEQ ID NO:157, SEQ ID NO:158, and SEQ ID NO:145;**
or
- (R) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of hPD-1 mAb 9(2.2), and respectively comprise the amino acid sequences: **SEQ ID NO:183, SEQ ID NO:172, and SEQ ID NO:173;** and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hPD-1 mAb 9(2.2), and, respectively comprise the amino acid sequences: **SEQ ID NO:188, SEQ ID NO:189, and SEQ ID NO:178.**

[0017d] In a fourth aspect, there is provided a composition comprising the multispecific anti-human PD-1-binding molecule of the third aspect and a pharmaceutically acceptable carrier.

[0017e] In a fifth aspect, there is provided an anti-human PD-1-binding monospecific monoclonal antibody that comprises a Variable Heavy Chain Domain and a Variable Light Chain Domain, wherein:

said Variable Heavy Chain Domain comprises a CDR_H1 Domain, a CDR_H2 Domain and a CDR_H3 Domain, and said Variable Light Chain Domain comprises a CDR_L1 Domain, a CDR_L2 Domain, and a CDR_L3 Domain, wherein:

- (A) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 1, and respectively comprise the amino acid sequences: **SEQ ID NO:71, SEQ ID NO:72, and SEQ ID NO:73;** and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 1, and respectively comprise the amino acid sequences: **SEQ ID NO:76, SEQ ID NO:77, and SEQ ID NO:78;**
or
- (B) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 2, and respectively comprise the

amino acid sequences: **SEQ ID NO:85**, **SEQ ID NO:86**, and **SEQ ID NO:87**; and

(2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 2, and, respectively comprise the amino acid sequences: **SEQ ID NO:90**, **SEQ ID NO:91**, and **SEQ ID NO:92**;

or

(C) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 3, and respectively comprise the amino acid sequences: **SEQ ID NO:99**, **SEQ ID NO:100**, and **SEQ ID NO:101**; and

(2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 3, and, respectively comprise the amino acid sequences: **SEQ ID NO:104**, **SEQ ID NO:105**, and **SEQ ID NO:106**;

or

(D) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 4, and respectively comprise the amino acid sequences: **SEQ ID NO:109**, **SEQ ID NO:110**, and **SEQ ID NO:111**; and

(2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 4, and, respectively comprise the amino acid sequences: **SEQ ID NO:114**, **SEQ ID NO:115**, and **SEQ ID NO:116**;

or

(F) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 6, and respectively comprise the amino acid sequences: **SEQ ID NO:129**, **SEQ ID NO:130**, and **SEQ ID NO:131**; and

(2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 6, and, respectively comprise the amino acid sequences: **SEQ ID NO:134**, **SEQ ID NO:135**, and **SEQ ID NO:136**;

or

(H) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 8, and respectively comprise the amino acid sequences: **SEQ ID NO:161**, **SEQ ID NO:162**, and **SEQ ID NO:163**; and

(2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 8, and, respectively comprise the amino acid sequences: **SEQ ID NO:166**, **SEQ ID NO:167**, and **SEQ ID NO:168**;

or

(I) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 9, and respectively comprise the amino acid sequences: **SEQ ID NO:171**, **SEQ ID NO:172**, and **SEQ ID NO:173**; and

- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 9, and, respectively comprise the amino acid sequences: **SEQ ID NO:176**, **SEQ ID NO:177**, and **SEQ ID NO:178**;
or
- (J) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 10, and respectively comprise the amino acid sequences: **SEQ ID NO:192**, **SEQ ID NO:193**, and **SEQ ID NO:194**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 10, and, respectively comprise the amino acid sequences: **SEQ ID NO:197**, **SEQ ID NO:198**, and **SEQ ID NO:199**;
or
- (K) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 11, and respectively comprise the amino acid sequences: **SEQ ID NO:202**, **SEQ ID NO:203**, and **SEQ ID NO:204**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 11, and, respectively comprise the amino acid sequences: **SEQ ID NO:207**, **SEQ ID NO:208**, and **SEQ ID NO:209**;
or
- (L) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 12, and respectively comprise the amino acid sequences: **SEQ ID NO:212**, **SEQ ID NO:213**, and **SEQ ID NO:214**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 12, and, respectively comprise the amino acid sequences: **SEQ ID NO:217**, **SEQ ID NO:218**, and **SEQ ID NO:219**;
or
- (M) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 13, and respectively comprise the amino acid sequences: **SEQ ID NO:222**, **SEQ ID NO:223**, and **SEQ ID NO:224**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 13, and, respectively comprise the amino acid sequences: **SEQ ID NO:227**, **SEQ ID NO:228**, and **SEQ ID NO:229**;
or
- (N) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 14, and respectively comprise the amino acid sequences: **SEQ ID NO:232**, **SEQ ID NO:233**, and **SEQ ID NO:234**; and

- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 14, and, respectively comprise the amino acid sequences: **SEQ ID NO:237**, **SEQ ID NO:238**, and **SEQ ID NO:239**;
or
- (O) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 15, and respectively comprise the amino acid sequences: **SEQ ID NO:242**, **SEQ ID NO:243**, and **SEQ ID NO:244**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 15, and, respectively comprise the amino acid sequences: **SEQ ID NO:247**, **SEQ ID NO:248**, and **SEQ ID NO:249**;
or
- (R) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of hPD-1 mAb 9(2.2), and respectively comprise the amino acid sequences: **SEQ ID NO:183**, **SEQ ID NO:172**, and **SEQ ID NO:173**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hPD-1 mAb 9(2.2), and, respectively comprise the amino acid sequences: **SEQ ID NO:188**, **SEQ ID NO:189**, and **SEQ ID NO:178**.

[0017f] In a sixth aspect, there is provided a composition comprising the anti-human PD-1-binding monospecific monoclonal antibody of the fifth aspect and a pharmaceutically acceptable carrier.

[0018] The disclosure further concerns the embodiments of all such anti-human PD-1-binding molecules wherein the molecule is an antibody, and especially wherein the molecule is a chimeric antibody or a humanized antibody.

[0019] The disclosure further concerns the embodiments of such anti-human PD-1-binding molecules wherein the Heavy Chain Variable Domain has the amino acid sequence of **SEQ ID NO:79**, **SEQ ID NO:93**, **SEQ ID NO:147**, **SEQ ID NO:149**, **SEQ ID NO:179**, **SEQ ID NO:181**, or **SEQ ID NO:250**.

[0020] The disclosure further concerns the embodiments of such anti-human PD-1-binding molecules wherein the Light Chain Variable Domain has the amino acid sequence of **SEQ ID NO:81**, **SEQ ID NO:95**, **SEQ ID NO:151**, **SEQ ID NO:153**, **SEQ ID NO:155**, **SEQ ID NO:184**, **SEQ ID NO:186**, or **SEQ ID NO:251**.

[0021] The disclosure further concerns the embodiment wherein the anti-human PD-1-binding molecule is a bispecific binding molecule, capable of simultaneously binding to human PD-1 and to a second epitope, and particularly concerns the embodiment wherein the second epitope is an epitope of a molecule involved in regulating an immune check point present on the surface of an immune cell (especially wherein the second epitope is an epitope of B7-H3,

B7-H4, BTLA, CD40, CD40L, CD47, CD70, CD80, CD86, CD94, CD137, CD137L, CD226, CTLA-4, Galectin-9, GITR, GITRL, HHLA2, ICOS, ICOSL, KIR, LAG-3, LIGHT, MHC class I or II, NKG2a, NKG2d, OX40, OX40L, PD1H, PD-1, PD-L1, PD-L2, PVR, SIRPa, TCR, TIGIT, TIM-3 or VISTA, and most particularly wherein the second epitope is an epitope of CD137, CTLA-4, LAG-3, OX40, TIGIT, or TIM-3).

[0022] The disclosure further concerns the embodiments wherein the anti-human PD-1-binding molecule is a bispecific molecule comprising a LAG-3 epitope-binding site, particularly wherein the LAG-3 epitope-binding site comprises:

- (A) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain of the Variable Heavy Chain of LAG-3 mAb 1, having the amino acid sequences: **SEQ ID NO:42**, **SEQ ID NO:43**, and **SEQ ID NO:44**, respectively; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of the Variable Light Chain of LAG-3 mAb 1, having the amino acid sequences: **SEQ ID NO:46**, **SEQ ID NO:47**, and **SEQ ID NO:48**, respectively;

or

- (B) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain of the Variable Heavy Chain of hLAG-3 mAb 1 VH1, having the amino acid sequences: **SEQ ID NO:42**, **SEQ ID NO:43**, and **SEQ ID NO:44**, respectively; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of the Variable Light Chain of hLAG-3 mAb 1 VL4, having the amino acid sequences: **SEQ ID NO:55**, **SEQ ID NO:47**, and **SEQ ID NO:48**, respectively;

or

- (C) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain of the Variable Heavy Chain of LAG-3 mAb 6, having the amino acid sequences: **SEQ ID NO:57**, **SEQ ID NO:58**, and **SEQ ID NO:59**, respectively; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of the Variable Light Chain of LAG-3 mAb 6, having the amino acid

sequences: **SEQ ID NO:61**, **SEQ ID NO:62**, and **SEQ ID NO:63**, respectively;

or

- (D) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain of the Variable Heavy Chain of hLAG-3 mAb 6 VH1, having the amino acid sequences: **SEQ ID NO:57**, **SEQ ID NO:58**, and **SEQ ID NO:59**, respectively; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain of the Variable Light Chain of LAG-3 mAb 6, having the amino acid sequences: **SEQ ID NO:298**, **SEQ ID NO:62**, and **SEQ ID NO:63**, respectively.

[0023] The disclosure further concerns the embodiment of such anti-human PD-1-binding molecules wherein the molecule is a diabody, and especially, wherein the diabody is a covalently bonded complex that comprises two, or three, or four, or five polypeptide chains. The disclosure further concerns the embodiment of such anti-human PD-1-binding molecules wherein the molecule is a trivalent binding molecule, and especially wherein the trivalent binding molecule is a covalently bonded complex that comprises three, four, five or more than five polypeptide chains. The disclosure additionally concerns the embodiment of such anti-human PD-1-binding molecules in which the molecule comprises an Fc Region. The disclosure additionally concerns the embodiment of such anti-human PD-1-binding molecules in which the molecule comprises an Albumin-Binding Domain, and especially a deimmunized Albumin-Binding Domain.

[0024] The disclosure further concerns the embodiments of all such anti-human PD-1-binding molecules wherein the molecule comprises an Fc Region, and wherein the Fc Region is a variant Fc Region that comprises one or more amino acid modifications that reduces the affinity of the variant Fc Region for an FcγR and/or enhances the serum half-life, and more particularly, wherein the modifications comprise at least one amino acid substitution selected from the group consisting of:

- (1) L234A; L235A;
- (2) L234A and L235A;
- (3) M252Y; M252Y and S254T;
- (4) M252Y and T256E;

(5) M252Y, S254T and T256E; or

(6) K288D and H435K;

wherein the numbering is that of the EU index as in Kabat.

[0025] The disclosure further concerns the embodiments in which any of the above-described PD-1-binding molecules is used to stimulate a T-cell mediate immune response. The disclosure additionally concerns the embodiments in which any of the above-described PD-1-binding molecules is used in the treatment of a disease or condition associated with a suppressed immune system, especially cancer or an infection.

[0025a] In a seventh aspect, there is provided use of the anti-human PD-1-binding monospecific monoclonal antibody of the first or the fifth aspect, or the multispecific anti-human PD-1-binding molecule of the third aspect, or the composition of the second, the fourth or the sixth aspect in the manufacture of a medicament for stimulating a T-cell mediate immune response of a subject in need thereof.

[0025b] In an eighth aspect, there is provided use of the anti-human PD-1-binding monospecific monoclonal antibody of the first or the fifth aspect, or the multispecific anti-human PD-1-binding molecule of the third aspect, or the composition of the second, the fourth or the sixth aspect in the manufacture of a medicament for the treatment of a disease or condition associated with a suppressed immune system.

[0026] The disclosure particularly concerns such use in the treatment or diagnosis or prognosis of cancer, wherein the cancer is characterized by the presence of a cancer cell selected from the group consisting of a cell of: an adrenal gland tumor, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, bladder cancer, bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a breast cancer, a carotid body tumors, a cervical cancer, a chondrosarcoma, a chordoma, a chromophobe renal cell carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a cutaneous benign fibrous histiocytoma, a desmoplastic small round cell tumor, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a fibrogenesis imperfecta ossium, a fibrous dysplasia of the bone, a gallbladder or bile duct cancer, gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, hepatocellular carcinoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia, a lipoma/benign lipomatous tumor, a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a medulloblastoma, a melanoma, a meningioma, a multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a neuroblastoma, a neuroendocrine tumors, an ovarian cancer, a pancreatic cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a pheochromocytoma, a pituitary tumor, a prostate cancer, a posterior uveal melanoma, a rare hematologic disorder, a renal metastatic cancer, a rhabdoid tumor, a rhabdomyosarcoma, a sarcoma, a skin cancer, a soft-tissue sarcoma, a squamous cell cancer, a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid metastatic cancer, and a uterine cancer.

[0027] The disclosure particularly concerns such use in the treatment or diagnosis or prognosis of cancer, wherein the cancer is colorectal cancer, hepatocellular carcinoma, glioma, kidney cancer, breast cancer, multiple myeloma, bladder cancer, neuroblastoma; sarcoma, non-

Hodgkin's lymphoma, non-small cell lung cancer, ovarian cancer, pancreatic cancer, a rectal cancer, acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), acute B lymphoblastic leukemia (B-ALL), chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), non-Hodgkin's lymphomas (NHL), including mantle cell leukemia (MCL), and small lymphocytic lymphoma (SLL), Hodgkin's lymphoma, systemic mastocytosis, or Burkitt's lymphoma.

[0028] The disclosure further concerns the embodiments in which any of the above-described PD-1-binding molecules is detectably labeled and is used in the detection of PD-1.

Brief Description of the Drawings

[0029] **Figure 1** provides a schematic of a representative covalently bonded diabody having two epitope-binding sites composed of two polypeptide chains, each having an E-coil or K-coil Heterodimer-Promoting Domain. A cysteine residue may be present in a linker and/or in the Heterodimer-Promoting Domain as shown in **Figure 3B**. VL and VH Domains that recognize the same epitope are shown using the same shading or fill pattern.

[0030] **Figure 2** provides a schematic of a representative covalently bonded diabody molecule having two epitope-binding sites composed of two polypeptide chains, each having a CH2 and CH3 Domain, such that the associated chains form all or part of an Fc Region. VL and VH Domains that recognize the same epitope are shown using the same shading or fill pattern.

[0031] **Figures 3A-3C** provide schematics showing representative tetravalent diabodies having four epitope-binding sites composed of two pairs of polypeptide chains (*i.e.*, four polypeptide chains in all). One polypeptide of each pair possesses a CH2 and CH3 Domain, such that the associated chains form all or part of an Fc Region. VL and VH Domains that recognize the same epitope are shown using the same shading or fill pattern. The two pairs of polypeptide chains may be same. In such embodiments wherein the VL and VH Domains recognize different epitopes (as shown in **Figures 3A-3C**), the resulting molecule possesses four epitope-binding sites and is bispecific and bivalent with respect to each bound epitope. In such embodiments wherein the VL and VH Domains recognize the same epitope (*e.g.*, the same VL Domain CDRs and the same VH Domain CDRs are used on both chains), the resulting molecule possesses four epitope-binding sites and is monospecific and tetravalent with respect to a single epitope. Alternatively, the two pairs of polypeptides may be different. In such

humanized VH Domain, designated herein as “**hPD-1 mAb 2 VH1**,” and one humanized VL Domains designated herein as “**hPD-1 mAb 1 VL1**.” An antibody comprising the humanized VL Domain paired with the humanized VH Domain is referred to as “**hPD-1 mAb 15**.”

[00185] The amino acid sequence of the VH Domain of hPD-1 mAb 15 VH1 (SEQ ID NO:250) is shown below (CDR_H residues are shown underlined):

EVQLVESGGG LVRPGGSLRL SCAASGFTFS SYLISWVRQA PGKGLEWVAA
ISGGGADTTY ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TATYYCARRG
TYAMDYWGQG TLVTVSS

[00186] An exemplary polynucleotide that encodes hPD-1 mAb 15 VH1 is SEQ ID NO:251 (nucleotides encoding the CDR_H residues are shown underlined):

gaagtgcaac tggttgaaag tggcggcggg ctggtgcggc caggtggttc
actcagactg tcttgtgcag cttcaggctt tacattctcc tcttatctta
tctcttgggt gcgccaagcc ccaggtgaagg gccttgaatg ggtcgccgcc
attagtgggg gtggtgccga tacatattat gccgacagcg tcaagggacg
tttcaccatc agcagggaca acgccaagaa tagcctttac ctgcagatga
actcacttag agctgaagac accgctactt attactgtgc ccggcgcggg
acttacgcta tggactattg gggccagggc accttgggtca ctgtctcatc c

[00187] The amino acid sequence of the VL Domain of hPD-1 mAb 15 VL1 (SEQ ID NO:252) is shown below (CDR_L residues are shown underlined):

DIQMTQSPSS LSASVGDRVIT ITCLASQTIG TWLAWYQQKP GKAPKLLIYA
ATSLADGVPS RFSGSGSGTD FTFTISSLQP EDFATYYCQQ LYSIPWTFGQ
GTKLEIK

[00188] An exemplary polynucleotide that encodes hPD-1 mAb 15 VL1 is SEQ ID NO:253 (nucleotides encoding the CDR_H residues are shown underlined):

gatatccaga tgaccagtc tcccagctct ctcagtgcga gcgtaggcga
ccgtgtgacc atcacctgtc tggccagtcga gaccattgga acctggctcg
cctgggtatca gcagaaacct ggcaaggccc ctaagctgct gatttacgcc
gccacctccc tcgcagatgg agtgccctcc cgatttagcg ggtccgggtc
cggcaccgac ttcacattca caatcagcag cctccagccc gaggatttcg
ctacatacta ctgtcaacag ctctactcca ttccatggac ctttgggtcag
ggtactaaac tggagatcaa a

V. Anti-Human PD-1 Antibodies PD-1 mAb 1-15, and Their Derivatives Having an Engineered Fc Region

[00189] In traditional immune function, the interaction of antibody-antigen complexes with cells of the immune system results in a wide array of responses, ranging from effector functions such as antibody dependent cytotoxicity, mast cell degranulation, and phagocytosis to

What Is Claimed Is:

Claim 1. An anti-human PD-1-binding monospecific monoclonal antibody that comprises a Variable Heavy Chain Domain and a Variable Light Chain Domain, wherein:

said Variable Heavy Chain Domain comprises a CDR_{H1} Domain, a CDR_{H2} Domain and a CDR_{H3} Domain, and said Variable Light Chain Domain comprises a CDR_{L1} Domain, a CDR_{L2} Domain, and a CDR_{L3} Domain, wherein:

- (A) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of PD-1 mAb 5, and respectively comprise the amino acid sequences: **SEQ ID NO:119**, **SEQ ID NO:120**, and **SEQ ID NO:121**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of PD-1 mAb 5, and, respectively comprise the amino acid sequences: **SEQ ID NO:124**, **SEQ ID NO:125**, and **SEQ ID NO:126**;

or

- (B) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of PD-1 mAb 7, and respectively comprise the amino acid sequences: **SEQ ID NO:139**, **SEQ ID NO:140**, and **SEQ ID NO:141**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of PD-1 mAb 7, and, respectively comprise the amino acid sequences: **SEQ ID NO:144**, **SEQ ID NO:145**, and **SEQ ID NO:146**;

or

- (C) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of hPD-1 mAb 7(1.2), and respectively comprise the amino acid sequences: **SEQ ID NO:139**, **SEQ ID NO:140**, and **SEQ ID NO:141**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of hPD-1 mAb 7(1.2), and, respectively

comprise the amino acid sequences: **SEQ ID NO:157**, **SEQ ID NO:145**, and **SEQ ID NO:146**;

or

- (D) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of hPD-1 mAb 7(1.3), and respectively comprise the amino acid sequences: **SEQ ID NO:139**, **SEQ ID NO:140**, and **SEQ ID NO:141**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hPD-1 mAb 7(1.3), and, respectively comprise the amino acid sequences: **SEQ ID NO:157**, **SEQ ID NO:158**, and **SEQ ID NO:145**.

- Claim 2. The anti-human PD-1-binding monospecific monoclonal antibody of claim 1, wherein said antibody is a chimeric antibody or a humanized antibody.
- Claim 3. The anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 1 or 2, wherein said antibody comprises a Heavy Chain Variable Domain that comprises the amino acid sequence of **SEQ ID NO:147** or **SEQ ID NO:149**.
- Claim 4. The anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 1-3, wherein said antibody comprises a Light Chain Variable Domain that comprises the amino acid sequence of **SEQ ID NO:151**, **SEQ ID NO:153** or **SEQ ID NO:155**.
- Claim 5. The anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 1-4, wherein said antibody comprises an Fc Region.
- Claim 6. The anti-human PD-1-binding monospecific monoclonal antibody of claim 5, wherein said Fc Region, is of the IgG1, IgG2, IgG3, or IgG4 isotype.
- Claim 7. The anti-human PD-1-binding monospecific monoclonal antibody of claim 6, wherein said antibody further comprises a Hinge Domain.

- Claim 8. The anti-human PD-1-binding monospecific monoclonal antibody of claim 7, wherein said Fc Region and said Hinge Domain are of the IgG4 isotype, and wherein said Hinge Domain comprises a stabilizing mutation.
- Claim 9. The anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 5-7, wherein said antibody comprises:
- (a) **SEQ ID NOs: 264 and 265;** or
 - (b) **SEQ ID NOs: 264 and 266.**
- Claim 10. The anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 5-8, wherein said Fc Region is a variant Fc Region that comprises:
- (a) one or more amino acid modifications that reduces the affinity of the variant Fc Region for an FcγR; and/or
 - (b) one or more amino acid modifications that enhances the serum half-life of the variant Fc Region.
- Claim 11. The anti-human PD-1-binding monospecific monoclonal antibody of claim 10, wherein said modifications that reduces the affinity of the variant Fc Region for an FcγR comprise the substitution of L234A; L235A; or L234A and L235A, wherein said numbering is that of the EU index as in Kabat.
- Claim 12. The anti-human PD-1-binding monospecific monoclonal antibody of claims 10 or 11, wherein said modifications that enhances the serum half-life of the variant Fc Region comprise the substitution of M252Y; M252Y and S254T; M252Y and T256E; M252Y, S254T and T256E; or K288D and H435K, wherein said numbering is that of the EU index as in Kabat.
- Claim 13. The anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 1-12, wherein said antibody is detectably labeled and is used in the detection of PD-1.
- Claim 14. A composition comprising the anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 1-12 and a pharmaceutically acceptable carrier.

- Claim 15. A multispecific anti-human PD-1-binding molecule that comprises a Variable Heavy Chain Domain and a Variable Light Chain Domain, wherein:
said Variable Heavy Chain Domain comprises a CDR_H1 Domain, a CDR_H2 Domain and a CDR_H3 Domain, and said Variable Light Chain Domain comprises a CDR_L1 Domain, a CDR_L2 Domain, and a CDR_L3 Domain, wherein:
- (A) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 1, and respectively comprise the amino acid sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**; and
 - (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 1, and respectively comprise the amino acid sequences: **SEQ ID NO:76**, **SEQ ID NO:77**, and **SEQ ID NO:78**;
or
 - (B) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 2, and respectively comprise the amino acid sequences: **SEQ ID NO:85**, **SEQ ID NO:86**, and **SEQ ID NO:87**; and
 - (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 2, and, respectively comprise the amino acid sequences: **SEQ ID NO:90**, **SEQ ID NO:91**, and **SEQ ID NO:92**;
or
 - (C) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 3, and respectively comprise the amino acid sequences: **SEQ ID NO:99**, **SEQ ID NO:100**, and **SEQ ID NO:101**; and
 - (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 3, and, respectively comprise the amino acid sequences: **SEQ ID NO:104**, **SEQ ID NO:105**, and **SEQ ID NO:106**;
or
 - (D) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 4, and respectively comprise the amino acid sequences: **SEQ ID NO:109**, **SEQ ID NO:110**, and **SEQ ID NO:111**; and
 - (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 4, and, respectively comprise the amino acid sequences: **SEQ ID NO:114**, **SEQ ID NO:115**, and **SEQ ID NO:116**;
or
 - (E) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 5, and respectively

- comprise the amino acid sequences: **SEQ ID NO:119**, **SEQ ID NO:120**, and **SEQ ID NO:121**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 5, and, respectively comprise the amino acid sequences: **SEQ ID NO:124**, **SEQ ID NO:125**, and **SEQ ID NO:126**;
- or
- (F) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 6, and respectively comprise the amino acid sequences: **SEQ ID NO:129**, **SEQ ID NO:130**, and **SEQ ID NO:131**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 6, and, respectively comprise the amino acid sequences: **SEQ ID NO:134**, **SEQ ID NO:135**, and **SEQ ID NO:136**;
- or
- (G) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 7, and respectively comprise the amino acid sequences: **SEQ ID NO:139**, **SEQ ID NO:140**, and **SEQ ID NO:141**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 7, and, respectively comprise the amino acid sequences: **SEQ ID NO:144**, **SEQ ID NO:145**, and **SEQ ID NO:146**;
- or
- (H) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 8, and respectively comprise the amino acid sequences: **SEQ ID NO:161**, **SEQ ID NO:162**, and **SEQ ID NO:163**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 8, and, respectively comprise the amino acid sequences: **SEQ ID NO:166**, **SEQ ID NO:167**, and **SEQ ID NO:168**;
- or
- (I) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 9, and respectively comprise the amino acid sequences: **SEQ ID NO:171**, **SEQ ID NO:172**, and **SEQ ID NO:173**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 9, and, respectively comprise the amino acid sequences: **SEQ ID NO:176**, **SEQ ID NO:177**, and **SEQ ID NO:178**;
- or

- (J) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 10, and respectively comprise the amino acid sequences: **SEQ ID NO:192**, **SEQ ID NO:193**, and **SEQ ID NO:194**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 10, and, respectively comprise the amino acid sequences: **SEQ ID NO:197**, **SEQ ID NO:198**, and **SEQ ID NO:199**;
- or
- (K) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 11, and respectively comprise the amino acid sequences: **SEQ ID NO:202**, **SEQ ID NO:203**, and **SEQ ID NO:204**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 11, and, respectively comprise the amino acid sequences: **SEQ ID NO:207**, **SEQ ID NO:208**, and **SEQ ID NO:209**;
- or
- (L) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 12, and respectively comprise the amino acid sequences: **SEQ ID NO:212**, **SEQ ID NO:213**, and **SEQ ID NO:214**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 12, and, respectively comprise the amino acid sequences: **SEQ ID NO:217**, **SEQ ID NO:218**, and **SEQ ID NO:219**;
- or
- (M) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 13, and respectively comprise the amino acid sequences: **SEQ ID NO:222**, **SEQ ID NO:223**, and **SEQ ID NO:224**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 13, and, respectively comprise the amino acid sequences: **SEQ ID NO:227**, **SEQ ID NO:228**, and **SEQ ID NO:229**;
- or
- (N) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 14, and respectively comprise the amino acid sequences: **SEQ ID NO:232**, **SEQ ID NO:233**, and **SEQ ID NO:234**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 14, and, respectively comprise the amino acid sequences: **SEQ ID NO:237**, **SEQ ID NO:238**, and **SEQ ID NO:239**;

- or
- (O) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 15, and respectively comprise the amino acid sequences: **SEQ ID NO:242, SEQ ID NO:243, and SEQ ID NO:244**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 15, and, respectively comprise the amino acid sequences: **SEQ ID NO:247, SEQ ID NO:248, and SEQ ID NO:249**;
- or
- (P) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of hPD-1 mAb 7(1.2), and respectively comprise the amino acid sequences: **SEQ ID NO:139, SEQ ID NO:140, and SEQ ID NO:141**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hPD-1 mAb 7(1.2), and, respectively comprise the amino acid sequences: **SEQ ID NO:157, SEQ ID NO:145, and SEQ ID NO:146**;
- or
- (Q) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of hPD-1 mAb 7(1.3), and respectively comprise the amino acid sequences: **SEQ ID NO:139, SEQ ID NO:140, and SEQ ID NO:141**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hPD-1 mAb 7(1.3), and, respectively comprise the amino acid sequences: **SEQ ID NO:157, SEQ ID NO:158, and SEQ ID NO:145**;
- or
- (R) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of hPD-1 mAb 9(2.2), and respectively comprise the amino acid sequences: **SEQ ID NO:183, SEQ ID NO:172, and SEQ ID NO:173**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hPD-1 mAb 9(2.2), and, respectively comprise the amino acid sequences: **SEQ ID NO:188, SEQ ID NO:189, and SEQ ID NO:178**.

Claim 16. The multispecific anti-human PD-1-binding molecule of claim 15, wherein said molecule comprises a Heavy Chain Variable Domain that comprises the amino acid sequence of **SEQ ID NO:79, SEQ ID NO:93, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:179, SEQ ID NO:181, or SEQ ID NO:250**.

- Claim 17. The multispecific anti-human PD-1-binding molecule of any one of claims 15-16, wherein said molecule comprises a Light Chain Variable Domain that comprises the amino acid sequence of **SEQ ID NO:81**, **SEQ ID NO:95**, **SEQ ID NO:151**, **SEQ ID NO:153**, **SEQ ID NO:155**, **SEQ ID NO:184**, **SEQ ID NO:186**, or **SEQ ID NO:252**.
- Claim 18. The multispecific anti-human PD-1-binding molecule of any one of claims 15-17, wherein said molecule is a bispecific binding molecule, capable of simultaneously binding to human PD-1 and to a second epitope.
- Claim 19. The multispecific anti-human PD-1-binding molecule of claim 18, wherein said second epitope is an epitope of a molecule involved in regulating an immune check point present on the surface of an immune cell.
- Claim 20. The multispecific anti-human PD-1-binding molecule of claim 19, wherein said second epitope is an epitope of B7-H3, B7-H4, BTLA, CD40, CD40L, CD47, CD70, CD80, CD86, CD94, CD137, CD137L, CD226, CTLA-4, Galectin-9, GITR, GITRL, HHLA2, ICOS, ICOSL, KIR, LAG-3, LIGHT, MHC class I or II, NKG2a, NKG2d, OX40, OX40L, PD1H, PD-1, PD-L1, PD-L2, PVR, SIRPa, TCR, TIGIT, TIM-3 or VISTA.
- Claim 21. The multispecific anti-human PD-1-binding molecule of claim 20, comprising a LAG-3 epitope-binding site, wherein said LAG-3 epitope-binding site comprises:
- (A) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain of the Variable Heavy Chain of LAG-3 mAb 1, and respectively comprise the amino acid sequences: **SEQ ID NO:42**, **SEQ ID NO:43**, and **SEQ ID NO:44**; and
 - (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of the Variable Light Chain of LAG-3 mAb 1, and respectively comprise the amino acid sequences: **SEQ ID NO:46**, **SEQ ID NO:47**, and **SEQ ID NO:48**;
- or
- (B) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain of the Variable Heavy Chain of hLAG-3 mAb 1 VH1, and

respectively comprise the amino acid sequences: **SEQ ID NO:42, SEQ ID NO:43, and SEQ ID NO:44**; and

- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain of the Variable Light Chain of LAG-3 mAb 1 VL4, and respectively comprise the amino acid sequences: **SEQ ID NO:55, SEQ ID NO:47, and SEQ ID NO:48**;

or

- (C) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain of the Variable Heavy Chain of LAG-3 mAb 6, and respectively comprise the amino acid sequences: **SEQ ID NO:57, SEQ ID NO:58, and SEQ ID NO:59**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain of the Variable Light Chain of LAG-3 mAb 6, and respectively comprise the amino acid sequences: **SEQ ID NO:61, SEQ ID NO:62, and SEQ ID NO:63**;

or

- (D) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain of the Variable Heavy Chain of hLAG-3 mAb 6 VH1, and respectively comprise the amino acid sequences: **SEQ ID NO:57, SEQ ID NO:58, and SEQ ID NO:59**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain of the Variable Light Chain of LAG-3 mAb 6, and respectively comprise the amino acid sequences: **SEQ ID NO:298, SEQ ID NO:62, and SEQ ID NO:63**.

Claim 22. The multispecific anti-human PD-1-binding molecule of any one of claims 15-21, wherein said molecule is:

- (A) a diabody, said diabody being a covalently bonded complex that comprises two, three, four or five polypeptide chains; or
- (B) a trivalent binding molecule, said trivalent binding molecule being a covalently bonded complex that comprises three, four or five polypeptide chains, or
- (C) a bispecific antibody.

- Claim 23. The multispecific anti-human PD-1-binding molecule of claim 22, wherein said molecule is a diabody and comprises an Albumin-Binding Domain (ABD).
- Claim 24. The multispecific anti-human PD-1-binding molecule of any one of claims 15-22, wherein said molecule comprises an Fc Region.
- Claim 25. The multispecific anti-human PD-1-binding molecule of claim 24, wherein said Fc Region, is of the IgG1, IgG2, IgG3, or IgG4 isotype.
- Claim 26. The multispecific anti-human PD-1-binding molecule of claim 25, wherein said molecule further comprises a Hinge Domain.
- Claim 27. The multispecific anti-human PD-1-binding molecule of claim 26, wherein said Fc Region and said Hinge Domain are of the IgG4 isotype, and wherein said Hinge Domain comprises a stabilizing mutation.
- Claim 28. The multispecific anti-human PD-1-binding molecule of any one of claims 24-27, wherein said Fc Region is a variant Fc Region that comprises:
- (a) one or more amino acid modifications that reduces the affinity of the variant Fc Region for an Fc γ R; and/or
 - (b) one or more amino acid modifications that enhances the serum half-life of the variant Fc Region.
- Claim 29. The multispecific anti-human PD-1-binding molecule of claim 28, wherein said modifications that reduces the affinity of the variant Fc Region for an Fc γ R comprise the substitution of L234A; L235A; or L234A and L235A, wherein said numbering is that of the EU index as in Kabat.
- Claim 30. The multispecific anti-human PD-1-binding molecule of claim 28 or 29, wherein said modifications that enhances the serum half-life of the variant Fc Region comprise the substitution of M252Y; M252Y and S254T; M252Y and T256E; M252Y, S254T and T256E; or K288D and H435K, wherein said numbering is that of the EU index as in Kabat.
- Claim 31. The multispecific anti-human PD-1-binding molecule of any one of claims 21, 23-29, wherein said molecule is a diabody comprising:

- (a) SEQ ID NO:267, wherein X₁ is Ala; X₂ is Tyr; X₃ is Thr; X₄ is Glu, and SEQ ID NO:268; or
- (b) SEQ ID NO:267, wherein X₁ is Gly; X₂ is Tyr; X₃ is Thr; X₄ is Glu, and SEQ ID NO:268; or
- (c) SEQ ID NO:267, wherein X₁ is Gly; X₂ is Met; X₃ is Ser; X₄ is Thr, and SEQ ID NO:268; or
- (d) SEQ ID NOs:269 and 270; or
- (e) SEQ ID NOs:271 and 272; or
- (f) SEQ ID NOs:273, 274, 275, and 276; or
- (g) SEQ ID NOs:277, 278, 279, and 280; or
- (h) SEQ ID NOs:281, 282, and 283; or
- (i) SEQ ID NOs:290 and 291; or
- (j) SEQ ID NOs:292 and 293.

Claim 32. The multispecific anti-human PD-1-binding molecule of any one of claims 15-31, wherein said molecule is detectably labeled and is used in the detection of PD-1.

Claim 33. A composition comprising the multispecific anti-human PD-1-binding molecule of any one of claims 15-31 and a pharmaceutically acceptable carrier.

Claim 34. An anti-human PD-1-binding monospecific monoclonal antibody that comprises a Variable Heavy Chain Domain and a Variable Light Chain Domain, wherein:

said Variable Heavy Chain Domain comprises a CDR_{H1} Domain, a CDR_{H2} Domain and a CDR_{H3} Domain, and said Variable Light Chain Domain comprises a CDR_{L1} Domain, a CDR_{L2} Domain, and a CDR_{L3} Domain, wherein:

- (A) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of PD-1 mAb 1, and respectively comprise the amino acid sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of PD-1 mAb 1, and respectively comprise the amino acid sequences: **SEQ ID NO:76**, **SEQ ID NO:77**, and **SEQ ID NO:78**;

or

- (B) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 2, and respectively comprise the amino acid sequences: **SEQ ID NO:85**, **SEQ ID NO:86**, and **SEQ ID NO:87**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 2, and, respectively comprise the amino acid sequences: **SEQ ID NO:90**, **SEQ ID NO:91**, and **SEQ ID NO:92**;
- or
- (C) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 3, and respectively comprise the amino acid sequences: **SEQ ID NO:99**, **SEQ ID NO:100**, and **SEQ ID NO:101**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 3, and, respectively comprise the amino acid sequences: **SEQ ID NO:104**, **SEQ ID NO:105**, and **SEQ ID NO:106**;
- or
- (D) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 4, and respectively comprise the amino acid sequences: **SEQ ID NO:109**, **SEQ ID NO:110**, and **SEQ ID NO:111**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 4, and, respectively comprise the amino acid sequences: **SEQ ID NO:114**, **SEQ ID NO:115**, and **SEQ ID NO:116**;
- or
- (F) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 6, and respectively comprise the amino acid sequences: **SEQ ID NO:129**, **SEQ ID NO:130**, and **SEQ ID NO:131**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 6, and, respectively comprise the amino acid sequences: **SEQ ID NO:134**, **SEQ ID NO:135**, and **SEQ ID NO:136**;
- or
- (H) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 8, and respectively comprise the amino acid sequences: **SEQ ID NO:161**, **SEQ ID NO:162**, and **SEQ ID NO:163**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 8, and, respectively comprise the amino acid sequences: **SEQ ID NO:166**, **SEQ ID NO:167**, and **SEQ ID NO:168**;

- or
- (I) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 9, and respectively comprise the amino acid sequences: **SEQ ID NO:171**, **SEQ ID NO:172**, and **SEQ ID NO:173**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 9, and, respectively comprise the amino acid sequences: **SEQ ID NO:176**, **SEQ ID NO:177**, and **SEQ ID NO:178**;
- or
- (J) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 10, and respectively comprise the amino acid sequences: **SEQ ID NO:192**, **SEQ ID NO:193**, and **SEQ ID NO:194**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 10, and, respectively comprise the amino acid sequences: **SEQ ID NO:197**, **SEQ ID NO:198**, and **SEQ ID NO:199**;
- or
- (K) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 11, and respectively comprise the amino acid sequences: **SEQ ID NO:202**, **SEQ ID NO:203**, and **SEQ ID NO:204**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 11, and, respectively comprise the amino acid sequences: **SEQ ID NO:207**, **SEQ ID NO:208**, and **SEQ ID NO:209**;
- or
- (L) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 12, and respectively comprise the amino acid sequences: **SEQ ID NO:212**, **SEQ ID NO:213**, and **SEQ ID NO:214**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 12, and, respectively comprise the amino acid sequences: **SEQ ID NO:217**, **SEQ ID NO:218**, and **SEQ ID NO:219**;
- or
- (M) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 13, and respectively comprise the amino acid sequences: **SEQ ID NO:222**, **SEQ ID NO:223**, and **SEQ ID NO:224**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 13, and, respectively

comprise the amino acid sequences: **SEQ ID NO:227**, **SEQ ID NO:228**, and **SEQ ID NO:229**;

or

- (N) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 14, and respectively comprise the amino acid sequences: **SEQ ID NO:232**, **SEQ ID NO:233**, and **SEQ ID NO:234**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 14, and, respectively comprise the amino acid sequences: **SEQ ID NO:237**, **SEQ ID NO:238**, and **SEQ ID NO:239**;

or

- (O) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of PD-1 mAb 15, and respectively comprise the amino acid sequences: **SEQ ID NO:242**, **SEQ ID NO:243**, and **SEQ ID NO:244**; and
- (2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of PD-1 mAb 15, and, respectively comprise the amino acid sequences: **SEQ ID NO:247**, **SEQ ID NO:248**, and **SEQ ID NO:249**;

or

- (R) (1) the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of hPD-1 mAb 9(2.2), and respectively comprise the amino acid sequences: **SEQ ID NO:183**, **SEQ ID NO:172**, and **SEQ ID NO:173**; and

(2) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hPD-1 mAb 9(2.2), and, respectively comprise the amino acid sequences: **SEQ ID NO:188**, **SEQ ID NO:189**, and **SEQ ID NO:178**.

Claim 35. The anti-human PD-1-binding monospecific monoclonal antibody of claim 34, wherein said antibody is a chimeric antibody or a humanized antibody.

Claim 36. The anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 34 or 35, wherein said antibody comprises a Heavy Chain Variable Domain that comprises the amino acid sequence of **SEQ ID NO:79**, **SEQ ID NO:93**, **SEQ ID NO:179**, **SEQ ID NO:181**, or **SEQ ID NO:250**.

Claim 37. The anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 34, 35 or 36, wherein said antibody comprises a Light Chain

Variable Domain that comprises the amino acid sequence of **SEQ ID NO:81**, **SEQ ID NO:95**, **SEQ ID NO:184**, **SEQ ID NO:186**, or **SEQ ID NO:252**.

- Claim 38. The anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 34-37, wherein said antibody comprises an Fc Region.
- Claim 39. The anti-human PD-1-binding monospecific monoclonal antibody of claim 38, wherein said Fc Region, is of the IgG1, IgG2, IgG3, or IgG4 isotype.
- Claim 40. The anti-human PD-1-binding monospecific monoclonal antibody of claim 39, wherein said antibody further comprises a Hinge Domain.
- Claim 41. The anti-human PD-1-binding monospecific monoclonal antibody of claim 40, wherein said Fc Region and said Hinge Domain are of the IgG4 isotype, and wherein said Hinge Domain comprises a stabilizing mutation.
- Claim 42. The anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 38-41, wherein said Fc Region is a variant Fc Region that comprises:
- (a) one or more amino acid modifications that reduces the affinity of the variant Fc Region for an FcγR; and/or
 - (b) one or more amino acid modifications that enhances the serum half-life of the variant Fc Region.
- Claim 43. The anti-human PD-1-binding monospecific monoclonal antibody of claim 42, wherein said modifications that reduces the affinity of the variant Fc Region for an FcγR comprise the substitution of L234A; L235A; or L234A and L235A, wherein said numbering is that of the EU index as in Kabat.
- Claim 44. The anti-human PD-1-binding monospecific monoclonal antibody of claim 42 or 43, wherein said modifications that that enhances the serum half-life of the variant Fc Region comprise the substitution of M252Y; M252Y and S254T; M252Y and T256E; M252Y, S254T and T256E; or K288D and H435K, wherein said numbering is that of the EU index as in Kabat.
- Claim 45. The anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 34-44, wherein said antibody is detectably labeled and is used in the detection of PD-1.

- Claim 46. A composition comprising the anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 34-44 and a pharmaceutically acceptable carrier.
- Claim 47. Use of the anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 1-13 or 34-45, or the multispecific anti-human PD-1-binding molecule of any one of claims 15-32, or the composition of any one of claims 14, 33 or 46 in the manufacture of a medicament for stimulating a T-cell mediate immune response of a subject in need thereof.
- Claim 48. Use of the anti-human PD-1-binding monospecific monoclonal antibody of any one of claims 1-13 or 34-45, or the multispecific anti-human PD-1-binding molecule of any one of claims 15-32, or the composition of any one of claims 14, 33 or 46 in the manufacture of a medicament for the treatment of a disease or condition associated with a suppressed immune system.
- Claim 49. The use of claim 48, wherein the disease or condition is cancer or an infection.
- Claim 50. The use of claim 49, wherein said cancer is characterized by the presence of a cancer cell selected from the group consisting of a cell of: an adrenal gland tumor, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, bladder cancer, bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a breast cancer, a carotid body tumors, a cervical cancer, a chondrosarcoma, a chordoma, a chromophobe renal cell carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a cutaneous benign fibrous histiocytoma, a desmoplastic small round cell tumor, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a fibrogenesis imperfecta ossium, a fibrous dysplasia of the bone, a gallbladder or bile duct cancer, gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, hepatocellular carcinoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia, a lipoma/benign lipomatous tumor, a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a medulloblastoma, a melanoma, a meningioma, a multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a neuroblastoma, a neuroendocrine tumors, an ovarian cancer, a pancreatic cancer, a papillary

thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a pheochromocytoma, a pituitary tumor, a prostate cancer, a posterior uveal melanoma, a rare hematologic disorder, a renal metastatic cancer, a rhabdoid tumor, a rhabdomyosarcoma, a sarcoma, a skin cancer, a soft-tissue sarcoma, a squamous cell cancer, a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid metastatic cancer, and a uterine cancer.