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(54) **HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS**

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(57)   **ABSTRACT**

The present invention provides isolated monoclonal antibodies, particularly human monoclonal antibodies, that specifically bind to PD-1 with high affinity. Nucleic acid molecules encoding the antibodies of the invention, expression vectors, host cells and methods for expressing the antibodies of the invention are also provided. Immunoconjugates, bispecific molecules and pharmaceutical compositions comprising the antibodies of the invention are also provided. The invention also provides methods for detecting PD-1, as well as methods for treating various diseases, including cancer and infectious diseases, using anti-PD-1 antibodies. The present invention further provides methods for using a combination immunotherapy, such as the combination of anti-CTLA-4 and anti-PD-1 antibodies, to treat hyperproliferative disease, such as cancer. The invention also provides methods for altering adverse events related to treatment with such antibodies individually.

Anti-PD1 17D8 VH

    V segment: 3-33
    D segment: unknown
    J segment: JH4b

```
         Q   V   Q   L   V   E   S   G   G   D   V   V   Q   P   G   G   S   L
    1   CAG GTG CAG CTG GTG GAG TCT GGG GGA GAC GTG GTC CAG CCT GGG GGG TCC CTG

                                                              CDR1
                                                   ~~~~~~~~~~~~~~~~~~
         R   L   S   C   A   A   S   G   V   A   F   S   N   Y   G   M   H   W
   55   AGA CTC TCC TGT GCA GCG TCT GGA GTC GCC TTC AGT AAC TAT GGC ATG CAC TGG

                                                              CDR2
                                                   ~~~~~~~~~~~~~~~~~~
         V   R   Q   A   P   G   K   G   L   E   W   V   A   V   I   W   Y   D
  109   GTC CGC CAG GCT CCC GGC AAG GGG CTG GAG TGG GTG GCA GTT ATC TGG TAT GAT

                          CDR2
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
         G   S   N   K   Y   Y   A   D   S   V   K   G   R   F   T   I   S   R
  163   GGA AGT AAT AAA TAC TAT GCA GAC TCC GTG AAG GGC CGG TTC ACC ATC TCC AGA


         D   N   S   K   N   M   L   Y   L   Q   M   N   S   L   R   A   E   D
  217   GAC AAT TCC AAG AAC ATG CTC TAT CTG CAA ATG AAC AGC CTG AGA GCC GAG GAC

                                      CDR3
                               ~~~~~~~~~~~~~~~~
         T   A   M   Y   Y   C   A   R   N   D   D   Y   W   G   Q   G   T   L
  271   ACG GCT ATG TAT TAC TGT GCG AGG AAC GAT GAC TAC TGG GGC CAG GGA ACC CTG

                                        └──→    JH4b

         V   T   V   S   S
  325   GTC ACC GTC TCC TCA
```

Figure 1A

Anti-PD1 17D8 VK

```
        V segment: L6
        J segment: JK4


          E    I    V    L    T    Q    S    P    A    T    L    S    L    S    P    G    E    R
     1   GAA ATT GTG TTG ACA CAG TCT CCA GCC ACC CTG TCT TTG TCT CCA GGG GAA AGA

                                                              CDR1
                                           ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
          A    T    L    S    C    R    A    S    Q    S    V    S    S    Y    L    A    W    Y
    55   GCC ACC CTC TCC TGC AGG GCC AGT CAG AGT GTT AGC AGC TAC TTA GCC TGG TAC

                                                                        CDR2
                                                                  ~~~~~~~~~~~~~~~~~~~~~
          Q    Q    K    P    G    Q    A    P    R    L    I    I    Y    D    A    S    N    R
   109   CAA CAG AAA CCT GGC CAG GCT CCC AGG CTC ATC ATC TAT GAT GCA TCC AAC AGG

         CDR2
         ~~~~~~~
          A    T    G    I    P    A    R    F    S    G    S    G    S    G    T    D    F    T
   163   GCC ACT GGC ATC CCA GCC AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC TTC ACT

                                                                             CDR3
                                                                          ~~~~~~~
          L    T    I    S    S    L    E    P    E    D    F    A    V    Y    Y    C    Q    Q
   217   CTC ACC ATC AGC AGC CTA GAG CCT GAA GAT TTT GCA GTT TAT TAC TGT CAG CAG

             CDR3
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~
          R    S    N    W    P    L    T    F    G    G    G    T    K    V    E    I    K
   271   CGT AGC AAC TGG CCT CTC ACT TTC GGC GGA GGG ACC AAG GTG GAG ATC AAA
```

Figure 1B

Anti-PD-1 2D3 VH

    V segment: 3-33
    D segment: 7-27
    J segment: JH4b

```
          Q    V    Q    L    V    E    S    G    G    D    V    V    Q    P    G    R    S    L
    1    CAG  GTG  CAG  CTG  GTG  GAA  TCT  GGG  GGA  GAC  GTG  GTC  CAG  CCT  GGG  AGG  TCC  CTG

                                                                            CDR1
                                                                       ~~~~~~~~~~~~~~~~~~~~
          R    L    S    C    A    A    S    G    L    T    F    T    N    Y    G    F    H    W
   55    AGA  CTC  TCC  TGT  GCA  GCG  TCT  GGA  TTA  ACC  TTC  ACT  AAC  TAT  GGC  TTC  CAC  TGG

                                                                            CDR2
                                                                       ~~~~~~~~~~~~~~~~~~~~~
          V    R    Q    A    P    G    K    G    L    E    W    V    A    V    I    W    Y    D
  109    GTC  CGC  CAG  GCT  CCA  GGC  AAG  GGG  CTG  GAG  TGG  GTG  GCT  GTT  ATA  TGG  TAT  GAT

                            CDR2
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
          G    S    K    K    Y    Y    A    D    S    V    K    G    R    F    T    I    S    R
  163    GGA  AGT  AAG  AAA  TAT  TAT  GCA  GAC  TCC  GTG  AAG  GGC  CGA  TTC  ACC  ATC  TCC  AGA

          D    N    S    K    N    T    L    Y    L    Q    M    N    N    L    R    A    E    D
  217    GAC  AAT  TCC  AAG  AAC  ACG  CTG  TAT  CTG  CAA  ATG  AAC  AAC  CTG  AGA  GCC  GAG  GAC

                                                      CDR3
                                                 ~~~~~~~~~~~~~~~~
          T    A    V    Y    Y    C    A    T    G    D    D    Y    W    G    Q    G    T    L
  271    ACG  GCT  GTG  TAT  TAC  TGT  GCG  ACT  GGG  GAT  GAC  TAC  TGG  GGC  CAG  GGA  ACC  CTG

          V    T    V    S    S
  325    GTC  ACC  GTC  TCC  TCA
```

Figure 2A

Anti-PD-1 2D3 VK

V segment: L6
J segment: JK4

```
        E   I   V   L   T   Q   S   P   A   T   L   S   L   S   P   G   E   R
    1  GAA ATT GTG TTG ACA CAG TCT CCA GCC ACC CTG TCT TTG TCT CCA GGG GAA AGA

                                                CDR1
                        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
        A   T   L   S   C   R   A   S   Q   S   V   S   S   Y   L   A   W   Y
   55  GCC ACC CTG TCC TGC AGG GCC AGT CAG AGT GTT AGC AGC TAC TTA GCC TGG TAC

                                                            CDR2
                                                    ~~~~~~~~~~~~~~~~~~~~
        Q   Q   K   P   G   Q   A   P   R   L   L   I   Y   D   T   S   N   R
  109  CAA CAG AAA CCT GGC CAG GCT CCC AGG CTC CTC ATC TAT GAT ACA TCC AAC AGG

        CDR2
        ~~~~~~~
        A   T   G   I   P   A   R   F   S   G   S   G   S   G   T   D   F   T
  163  GCC ACT GGC ATC CCA GCC AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC TTC ACT

                                                            CDR3
                                                            ~~~~~~~
        L   T   I   S   S   L   E   P   E   D   F   A   V   Y   Y   C   Q   Q
  217  CTC ACC ATC AGC AGC CTA GAG CCT GAA GAT TTT GCA GTT TAT TAC TGT CAG CAG

        CDR3
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~
        R   S   N   W   P   L   T   F   G   G   G   T   K   V   E   I   K
  271  CGT AGC AAC TGG CCG CTC ACT TTC GGC GGA GGG ACC AAG GTG GAG ATC AAA
```

Figure 2B

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