from the same subject while being in a different stage of the disease or is determined from clinical data of a large population of subjects.

According to another aspect, the present invention provides an isolated monoclonal antibody which binds to human poliovirus receptor (PVR), or an antibody fragment thereof comprising at least the antigen binding portion, wherein the isolated antibody or antibody fragment comprises:

(i) a CDR set of six CDRs wherein: HC CDR1 is SNYWIE (SEQ ID NO: 84); HC CDR2 is EIFPGSGRINFNEKFKG (SEQ ID NO: 38); HC CDR3 is TKIYGNSFDY (SEQ ID NO: 40); LC CDR1 is KASQDVGTAV (SEQ ID NO: 85); LC CDR2 is WASSRHN (SEQ ID NO: 46); and LC CDR3 is QQYSRYPLT (SEQ ID NO: 48); or

(ii) a CDR set of six CDRs wherein: HC CDR1 is RYWMT (SEQ ID NO: 80); HC CDR2 is EIHPDSSKINYTPSQKD (SEQ ID NO: 81); HC CDR3 is PDGNYNALDY (SEQ ID NO: 82); LC CDR1 is KASQDVGTAVT (SEQ ID NO: 12); LC CDR2 is WASTRHT (SEQ ID NO: 14); and LC CDR3 is QQYSRYPYT (SEQ ID NO: 16); or

(iii) a CDR set of six CDRs wherein: HC CDR1 is EYTMH (SEQ ID NO: 83); HC CDR2 is GIDPNNGGTNYNQNFKG (SEQ ID NO: 22); HC CDR3 is VIPLEY (SEQ ID NO: 24); LC CDR1 is KASQNVYTNVA (SEQ ID NO: 28); LC CDR2 is SASYRYR (SEQ ID NO: 30); and LC CDR3 is QQYNSYPLA (SEQ ID NO: 32).

According to another aspect, the present invention provides a polynucleotide sequence encoding a heavy chain variable region of the monoclonal antibody as described herein, and a polynucleotide sequence encoding a light chain variable region of said monoclonal antibody.

According to another aspect, the present invention provides a plasmid comprising at least one polynucleotide sequence as described herein.

According to another aspect, the present invention provides a hybridoma cell comprising a polynucleotide sequence encoding a heavy chain variable region of the monoclonal antibody as described herein, and a polynucleotide sequence encoding a light chain variable region of said monoclonal antibody.

CLAIMS

1. An isolated monoclonal antibody which binds to human poliovirus receptor (PVR), or an antibody fragment thereof comprising at least the antigen binding portion, wherein the isolated antibody or antibody fragment comprises:
   (i) a CDR set of six CDRs wherein: HC CDR1 is SNYWIE (SEQ ID NO: 84); HC CDR2 is EIFPGSGRINFNEKFKG (SEQ ID NO: 38); HC CDR3 is TKIYGNSFDY (SEQ ID NO: 40); LC CDR1 is KASQDVGTAV (SEQ ID NO: 85); LC CDR2 is WASSRHN (SEQ ID NO: 46); and LC CDR3 is QQYSRYPLT (SEQ ID NO: 48); or
   (ii) a CDR set of six CDRs wherein: HC CDR1 is RYWMT (SEQ ID NO: 80); HC CDR2 is EIHPDSSKINYTPSQKD (SEQ ID NO: 81); HC CDR3 is PDGNYNALDY (SEQ ID NO: 82); LC CDR1 is KASQDVGTAVT (SEQ ID NO: 12); LC CDR2 is WASTRHT (SEQ ID NO: 14); and LC CDR3 is QQYSRYPYT (SEQ ID NO: 16); or
   (iii) a CDR set of six CDRs wherein: HC CDR1 is EYTMH (SEQ ID NO: 83); HC CDR2 is GIDPNNGGTNYNQNFKG (SEQ ID NO: 22); HC CDR3 is VIPLEY (SEQ ID NO: 24); LC CDR1 is KASQNVYTNVA (SEQ ID NO: 28); LC CDR2 is SASYRYR (SEQ ID NO: 30); and LC CDR3 is QQYNSYPLA (SEQ ID NO: 32).
2. The isolated monoclonal antibody or the antibody fragment according to claim 1, comprising a heavy chain variable region selected from SEQ ID NO: 34 and SEQ ID NO: 77.
3. The isolated monoclonal antibody or the antibody fragment according to any one of claims 1 or 2, comprising a light chain variable region sequence selected from SEQ ID NO: 42 and SEQ ID NO: 79.
4. The isolated monoclonal antibody or the antibody fragment according to any one of claims 1 to 3, comprising a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 34 and the light chain comprises SEQ ID NO: 42.
5. The isolated monoclonal antibody or the antibody fragment according to any one of claims 1 to 3, comprising a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 77 and the light chain comprises SEQ ID NO: 79.

6. The isolated monoclonal antibody or the antibody fragment according to claim 1, comprising a heavy chain variable region selected from SEQ ID NO: 2 and SEQ ID NO: 69.

7. The isolated monoclonal antibody or the antibody fragment according to any one of claims 1 or 6, comprising a light chain variable region selected from SEQ ID NO: 10 and SEQ ID NO: 71.

8. The isolated monoclonal antibody or the antibody fragment according to any one of claims 1, 6, or 7, comprising a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 2 and the light chain comprises SEQ ID NO: 10.

9. The isolated monoclonal antibody or the antibody fragment according to any one of claims 1, 6 or 7, comprising a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 69 and the light chain comprises SEQ ID NO: 71.

10. The isolated monoclonal antibody or the antibody fragment according to claim 1, comprising a heavy chain variable region selected from SEQ ID NO: 18 and SEQ ID NO: 73.

11. The isolated monoclonal antibody or the antibody fragment according to any one of claim 1 or 10, comprising a light chain variable sequence selected from SEQ ID NO: 26 and SEQ ID NO: 75.

12. The isolated monoclonal antibody or the antibody fragment according to any one of claims 1, 10 or 11, comprising a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 18 and the light chain comprises SEQ ID NO: 26.

13. The isolated monoclonal antibody or the antibody fragment according to any one of claims 1, 10 or 11, comprising a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 73 and the light chain comprises SEQ ID NO: 75.

14. The isolated monoclonal antibody according to any one of claims 1 to 13 capable of inhibit binding of PVR to T cell immunoreceptor with Ig and ITIM domains (TIGIT).

15. A polynucleotide sequence encoding a heavy chain variable region of the monoclonal antibody according to any one of claims 1-13, and a polynucleotide sequence encoding a light chain variable region of said monoclonal antibody.

16. The polynucleotide sequence of claim 15, comprising a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 68, SEQ ID NO: 17, SEQ ID NO: 72, SEQ ID NO: 33 and SEQ ID NO: 76.

17. The polynucleotide sequence of claim 15, comprising a sequence selected from the group consisting of: SEQ ID NO: 70, SEQ ID NO: 74, and SEQ ID NO: 78.

18. A plasmid comprising at least one polynucleotide sequence according to any one of claims 15 to 17.

19. A hybridoma cell comprising a polynucleotide sequence encoding a heavy chain variable region of the monoclonal antibody according to any one of claims 1-13, and a polynucleotide sequence encoding a light chain variable region of said monoclonal antibody.

20. The monoclonal antibody according to any one of claims 1 to 13 attached to a cytotoxic moiety, a radioactive moiety, or an identifiable moiety.

21. A pharmaceutical composition comprising, as an active ingredient, the at least one isolated antibody or fragment thereof according to any one of claims 1 to 13 and 20, and a pharmaceutical acceptable excipient, diluent, salt or carrier.

22. The pharmaceutical composition of claim 21 for use in modulating the immune system by inhibiting binding of PVR to TIGIT.

23. The pharmaceutical composition of claim 21 for use in treating cancer.

24. The pharmaceutical composition of claim 21 for use in preventing or treating a viral infection in a subject.

25. The pharmaceutical composition of claim 21 for use in treating an angiogenesis-related disease or disorder.

26. The pharmaceutical composition of claim 25, wherein the angiogenesis-related disease or disorder is selected from the group consisting of: cancer, cell proliferative diseases of the eye, retinal disorders, and inflammatory diseases.

27. Use of a pharmaceutical composition according to claim 21 in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a subject in need thereof.

28. The use of claim 27 further comprising an additional anti-cancer therapy selected from surgery, chemotherapy, radiotherapy, and immunotherapy.

29. The use of claim 27 wherein an additional immuno-modulator, activated lymphocyte cell, kinase inhibitor, chemotherapeutic agent or any other anti-cancer agent is to be further administered to said subject.

30. The use of claim 29, wherein the additional immune-modulator is an antibody against an immune checkpoint molecule selected from the group consisting of PD-1, CTLA-4,

PDL-1, CEACAM1, NKG2A, B7-H3, B7-H4, VISTA, CD112R, lymphocyte activation gene 3 (LAG3), CD137, OX40 (also referred to as CD134), killer cell immunoglobulin-like receptors (KIR), TIGIT, and any combination thereof.

31. The use of claim 27, wherein the cancer is a solid cancer.

32. The use of claim 27, wherein the cancer is a hematological cancer.

33. The use of claim 27, wherein said use results in preventing or reducing metastases formation, growth or spread in a subject.

34. A method of *in vitro* diagnosing a cancer in a subject, the method comprising contacting a biological sample with an antibody or antibody fragment according to any one of claims 1 to 13.

35. A kit for diagnosing a cancer in a subject comprising at least one antibody or antibody fragment according to any one of claims 1 to 13.