

In some examples, the PD-L1 axis binding antagonist is a PD-1 binding antagonist. In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to one or more of its ligand binding partners.

In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1.
In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2.
In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and

PD-L2.
In some examples, the PD-1 binding antagonist is an antibody or antigen-binding fragment thereof.

In some examples, the antibody is selected from the group consisting of: MDX-1106 (nivolumab), MK-3475 (pembrolizumab), MEDI-0680 (AMP-514), PDR001, REGN2810, and BGB-108.

In some examples, the PD-1 binding antagonist is an Fc-fusion protein.

~~In one aspect, the present disclosure provides use of an agonist of CD177 activity in the manufacture of a medicament for treating an individual having a cancer.~~

In another aspect, the present disclosure provides use of an agonist of CD177 activity in the manufacture of a medicament for treating an individual having a cancer, wherein the agonist of CD177 activity is a small molecule, an antibody or antigen-binding fragment thereof that binds CD177, a peptide, or a mimic, wherein the use comprises determining an expression level of podoplanin (PDPN) in a sample that has been obtained from the individual, wherein the expression level of PDPN in the sample is above a reference PDPN expression level in a population of individuals having a cancer, wherein the sample that has been obtained from the individual is a tumor tissue sample or a tumor fluid sample, and wherein an effective amount of the agonist of CD177 is to be administered to the individual.

~~In yet another aspect, the present disclosure provides use of an agonist of CD177 activity in the manufacture of a medicament for treating an individual having a cancer, wherein an expression level of PDPN in a sample that has been obtained from the individual has been determined to be above a reference PDPN expression level.~~

In another example, the disclosure features a method of treating an individual having a cancer comprising administering to the individual an effective amount of an agonist of CD177 activity.

In another example, the disclosure features a method of identifying an individual having a cancer who may benefit from a treatment comprising an agonist of CD177 activity, the method comprising determining an expression level of podoplanin (PDPN) in a sample from the individual, wherein an expression level of PDPN in the sample that is above a reference PDPN expression level identifies the individual as one who may benefit from a treatment comprising an agonist of CD177 activity.

In one aspect, the present disclosure provides a method of identifying an individual having a cancer who may benefit from a treatment comprising an agonist of CD177 activity, wherein the agonist of CD177 activity is a small molecule, an antibody or antigen-binding fragment thereof that binds CD177, a peptide, or a mimic, the method comprising determining an expression level of PDPN in a sample that has been obtained from the individual, wherein an expression level of PDPN in the sample that is above a reference PDPN expression level in a population of individuals having a cancer identifies the individual as one who may benefit from the treatment comprising the agonist of CD177 activity, and wherein the sample that has been obtained from the individual is a tumor tissue sample or a tumor fluid sample.

In another example, the disclosure features a method of selecting a therapy for an individual having a cancer, the method comprising determining an expression level of PDPN in a sample from the individual, wherein an expression level of PDPN in the sample that is above a reference PDPN expression level identifies the individual as one who may benefit from a treatment comprising an agonist of CD177 activity.

In another aspect, the present disclosure provides a method of selecting a therapy for an individual having a cancer, the method comprising determining an expression level of PDPN in a sample that has been obtained from the individual, wherein an expression level of PDPN in the sample that is above a reference PDPN expression level in a population of individuals having a cancer identifies the individual as one who may benefit from a treatment comprising an agonist of CD177 activity, wherein the agonist of CD177 activity is a small molecule, an antibody or antigen-binding fragment thereof that binds CD177, a peptide, or a mimic, and wherein the sample that has been obtained from the individual is a tumor tissue sample or a tumor fluid sample.

In some examples, the individual has an expression level of PDPN in the sample that is above a reference PDPN expression level and the method further comprises administering to the individual an effective amount of an agonist of CD177 activity.

In another example, the disclosure features a method of treating an individual having a cancer, the method comprising (a) determining an expression level of PDPN in a sample from the individual, wherein the expression level of PDPN in the sample is above a reference PDPN expression level; and (b) administering to the individual an effective amount of an agonist of CD177 activity.

In another example, the disclosure features a method of treating an individual having a cancer, the method comprising administering to the individual an effective amount of an agonist of CD177 activity, wherein the expression level of PDPN in a sample from the individual has been determined to be above a reference PDPN expression level.

In some examples, the CD177 activity is inhibition of PDPN.

In some examples, the sample from the individual is a tumor tissue sample or a tumor fluid sample. In some examples, the tumor tissue sample is a formalin-fixed and paraffin-embedded (FFPE) sample, an archival sample, a fresh sample, or a frozen sample.

In some examples, the expression level of PDPN in the sample is a protein expression level of PDPN or an RNA expression level of PDPN. In some examples, the expression level of PDPN in the sample

WHAT IS CLAIMED IS:

~~1.—Use of an agonist of CD177 activity in the manufacture of a medicament for treating an individual having a cancer.~~

~~2.1.~~ Use of an agonist of CD177 activity in the manufacture of a medicament for treating an individual having a cancer, wherein the agonist of CD177 activity is a small molecule, an antibody or antigen-binding fragment thereof that binds CD177, a peptide, or a mimic, wherein the use comprises determining an expression level of podoplanin (PDPN) in a sample that has been obtained from the individual, wherein the expression level of PDPN in the sample is above a reference PDPN expression level in a population of individuals having a cancer, wherein the sample that has been obtained from the individual is a tumor tissue sample or a tumor fluid sample, and wherein an effective amount of the agonist of CD177 is to be administered to the individual.

~~3.—Use of an agonist of CD177 activity in the manufacture of a medicament for treating an individual having a cancer, wherein an expression level of PDPN in a sample that has been obtained from the individual has been determined to be above a reference PDPN expression level.~~

~~4.2.~~ A method of identifying an individual having a cancer who may benefit from a treatment comprising an agonist of CD177 activity, wherein the agonist of CD177 activity is a small molecule, an antibody or antigen-binding fragment thereof that binds CD177, a peptide, or a mimic, the method comprising determining an expression level of PDPN in a sample that has been obtained from the individual, wherein an expression level of PDPN in the sample that is above a reference PDPN expression level in a population of individuals having a cancer identifies the individual as one who may benefit from the treatment comprising the agonist of CD177 activity, and wherein the sample that has been obtained from the individual is a tumor tissue sample or a tumor fluid sample.

~~5.3.~~ A method of selecting a therapy for an individual having a cancer, the method comprising determining an expression level of PDPN in a sample that has been obtained from the individual, wherein an expression level of PDPN in the sample that is above a reference PDPN expression level in a population of individuals having a cancer identifies the individual as one who may benefit from a treatment comprising an agonist of CD177 activity, wherein the agonist of CD177 activity is a small molecule, an antibody or antigen-binding fragment thereof that binds CD177, a peptide, or a mimic, and wherein the sample that has been obtained from the individual is a tumor tissue sample or a tumor fluid sample.

~~6.4.~~ The method of claim ~~4-2~~ or ~~53~~, wherein the individual has an expression level of PDPN in the sample that is above the reference PDPN expression level and wherein an effective amount of the agonist of CD177 activity is to be administered to the individual.

~~7.5.~~ The use of ~~any one of claims 1-3 claim 1~~ or the method of any one of claims ~~42-46~~, wherein the CD177 activity is inhibition of PDPN.

~~8. The use of claim 2 or 3, the method of any one of claims 4-6 or the use or method of claim 7, wherein the sample that has been obtained from the individual is a tumor tissue sample or a tumor fluid sample.~~

~~9-6.~~ The use of claim 1 or method of any one of claims 82-4 or the use or method of claim 5, wherein the tumor tissue sample is a formalin-fixed and paraffin-embedded (FFPE) sample, an archival sample, a fresh sample, or a frozen sample.

~~10-7.~~ The use of claim ~~2 or 31~~, the method of any one of claims ~~42-64~~, or the use or method of any one of claims 7-9 claim 5 or 6, wherein the expression level of PDPN in the sample is a protein expression level of PDPN or an RNA expression level of PDPN.

~~11-8.~~ The use or method of claim ~~107~~, wherein the expression level of PDPN in the sample is an RNA expression level of PDPN.

~~12-9.~~ The use or method of claim ~~118~~, wherein the RNA expression level of PDPN is determined by *in situ* hybridization (ISH), RNA-seq, RT-qPCR, qPCR, multiplex qPCR or RT-qPCR, microarray analysis, SAGE, MassARRAY technique, FISH, or a combination thereof.

~~13. The use of claim 2 or 3, the method of any one of claims 4-6, or the use or method of any one of claims 7-12, wherein the reference PDPN expression level is an expression level of PDPN in a population of individuals having a cancer.~~

~~14. The use or method of claim 13, wherein the cancer is a colorectal cancer (CRC), a squamous cell carcinoma of the head and neck, or a glioma.~~

~~15-10.~~ The use of claim 1, the method of any one of claims 2-4, or the use or method of any one of claims 13 or 145-9, wherein the reference PDPN expression level is the 50th percentile of expression levels in the population.

~~16-11.~~ The use of claim 1, the method of any one of claims 2-4, or the use or method of any one of claims 13 or 145-9, wherein the reference PDPN expression level is the 66th percentile of expression levels in the population.

~~17-12.~~ The use of claim ~~12 or 3~~, the method of any one of claims ~~42-64~~, or the use or method of any one of claims ~~75-1611~~, wherein the reference PDPN expression level is a pre-assigned PDPN expression level.

18.13. The use of ~~any one of claims 1-3~~ claim 1 or the method of any one of claims ~~42-64~~, or the use or method of any one of claims ~~75-1712~~, wherein the cancer is a CRC, a squamous cell carcinoma of the head and neck, or a glioma.

19.14. The use or method of claim ~~1813~~, wherein the cancer is a CRC.

20.15. The use or method of claim ~~1914~~, wherein the CRC is a stage II CRC.

21.16. The use or method of claim ~~1914~~, wherein the CRC is a stage IV CRC.

22.17. The method of any one of claims ~~42-2416~~, wherein the benefit comprises an extension in the individual's recurrence-free survival (RFS) as compared to treatment without the agonist of CD177 activity.

23.18. The use or method of any one of claims 1-~~2317~~, wherein the agonist of CD177 activity results in an increase in the binding of PDPN and CD177 relative to binding of the two proteins in the absence of the agonist.

24.19. The use or method of any one of claims 1-~~2318~~, wherein the agonist of CD177 activity results in a change in a downstream activity of PDPN relative to the downstream activity in the absence of the agonist of CD177 activity.

25.20. The use or method of claim ~~2419~~, wherein the change in the downstream activity is a decrease in tumor growth.

26.21. The use or method of claim ~~2419~~, wherein the change in the downstream activity is a decrease in cancer-associated fibroblast (CAF) contractility.

~~27. The use or method of any one of claims 1-26, wherein the agonist of CD177 activity is a small molecule, an antibody or antigen-binding fragment thereof, a peptide, or a mimic.~~

28.22. The use or method of ~~any one of~~ claims 271-21, wherein the agonist of CD177 activity is a peptide.

29.23. The use or method of claim ~~2822~~, wherein the peptide is a CD177 peptide.

30.24. The use or method of claim ~~2923~~, wherein the CD177 peptide is an extracellular domain of CD177.

31.25. The use or method of claim ~~3024~~, wherein the peptide is multimerized.

~~32-26.~~_____ The use or method of claim ~~31-25~~, wherein the peptide is tetramerized.

~~33-27.~~_____ The use or method of claim ~~32-26~~, wherein the peptide is tetramerized using streptavidin.

~~34. The use or method of claim 27, wherein the agonist of CD177 activity is an antibody or antigen-binding fragment thereof.~~

~~35. The use or method of claim 34, wherein the antibody or antigen-binding fragment thereof binds PDPN.~~

~~36. The use or method of claim 35, wherein the antibody or antigen-binding fragment thereof is an antagonist antibody or antigen-binding fragment thereof.~~

~~37-28.~~_____ The use or method of any one of claims 341-21, wherein the agonist of CD177 activity is an antibody or antigen-binding fragment thereof that binds CD177.

~~38-29.~~_____ The use or method of claim ~~37-28~~, wherein the antibody or antigen-binding fragment thereof is an agonist antibody or antigen-binding fragment thereof.

~~39-30.~~_____ The use or method of any one of claims ~~27-1-21~~ and ~~34-38-28-29~~, wherein the antigen-binding fragment is a bis-Fab, an Fv, a Fab, a Fab'-SH, a F(ab')₂, a diabody, a linear antibody, an scFv, an ScFab, a VH domain, or a VHH domain.

~~40-31.~~_____ The use or method of any one of claims 1-~~39-30~~, wherein the individual is a human.