

metastatic pancreatic cancer, such as pancreatic cancer having metastasized to the liver and/or lung, and Microsatellite Stable (MSS) pancreatic cancer, in a subject comprising administering to the subject 2, 3, or 4 mg/kg of an anti-CSF1R antibody once every two weeks and 400-600 mg an anti-PD-1 antibody once every four weeks, wherein the anti-CSF1R antibody comprises a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 5, an HC CDR2 having the sequence of SEQ ID NO: 6, and an HC CDR3 having the sequence of SEQ ID NO: 7, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 8, a LC CDR2 having the sequence of SEQ ID NO: 9, and a LC CDR3 having the sequence of SEQ ID NO: 10; and wherein the anti-PD-1 antibody comprises a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 28, an HC CDR2 having the sequence of SEQ ID NO: 30, and an HC CDR3 having the sequence of SEQ ID NO: 32, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 35, a LC CDR2 having the sequence of SEQ ID NO: 37, and a LC CDR3 having the sequence of SEQ ID NO: 39. In one aspect, the present disclosure refers to use of an anti-CSF1R antibody and an anti-PD-1 antibody for preparation of a medicament for treatment of pancreatic cancer in a subject, wherein the cancer has been determined to be microsatellite-stable (MSS), and wherein the cancer has been determined to have a tumor mutation burden (TMB) of ~~less than 20 mutations/megabase, less than 15 mutations/megabase, or~~ less than 10 mutations/megabase, as determined with ~~the FICDx assay~~ a next-generation sequencing assay, and/or wherein the cancer has been determined to have a TMB of less than ~~400, less than 300 or less than~~ 200 missense mutations as determined by whole exome sequencing (WES), and wherein the anti-CSF1R antibody is to be administered to the subject at a dose of ~~2, 3,~~ or 4 mg/kg once every two weeks and the anti-PD-1 antibody is to be administered to the subject at a dose of 400-600 mg once every four weeks, wherein the anti-CSF1R antibody comprises a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 5, an HC CDR2 having the sequence of SEQ ID NO: 6, and an HC CDR3 having the sequence of SEQ ID NO: 7, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 8, a LC CDR2 having the sequence of SEQ ID NO: 9, and a LC CDR3 having the sequence of SEQ ID NO: 10; and wherein the anti-PD-1 antibody comprises a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 28, an HC CDR2 having the sequence of SEQ ID NO: 30, and an HC CDR3 having the sequence of SEQ ID NO: 32, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 35, a LC CDR2 having the sequence of SEQ ID NO: 37, and a LC CDR3 having the sequence of SEQ ID NO: 39.

[014] In some examples, the subject is administered 4 mg/kg of the anti-CSF1R antibody once every two weeks and 450-500 mg the anti-PD-1 antibody once every four weeks. In some examples, the subject is administered 4 mg/kg of the anti-CSF1R antibody once every two weeks and 480 mg the anti-PD-1 antibody once every four weeks.

[015] In some examples, the anti-CSF1R antibody comprises full length heavy and/or light chains, or is a Fab, an Fv, an scFv, a Fab', or a (Fab')₂ fragment. In some examples, the anti-PD-1 antibody comprises full length heavy and/or light chains, or is a Fab, an Fv, an scFv, a Fab', or a (Fab')₂ fragment. In some examples, the anti-PD-1 antibody heavy chain comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 23 and wherein the anti-PD-1 antibody light chain comprises a light chain variable region comprising the sequence of SEQ ID NO: 25. In some examples, the anti-PD-1 antibody comprises a heavy chain comprising the sequence of each of SEQ ID NOs: 23 and 24 and wherein the anti-PD-1 antibody comprises a light chain comprising the sequence of each of SEQ ID NOs: 25 and 26. In some examples, the anti-PD-1 antibody is nivolumab, pembrolizumab, or PDR001. In some examples, the anti-CSF1R antibody comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 11 and wherein the anti-

CLAIMS

1. Use of an anti-CSF1R antibody and an anti-PD-1 antibody for preparation of a medicament for treatment of pancreatic cancer in a subject,
wherein the cancer has been determined to be microsatellite-stable (MSS), and
wherein the cancer has been determined to have a tumor mutation burden (TMB) of ~~less than 20 mutations/megabase, less than 15 mutations/megabase, or~~ less than 10 mutations/megabase, as determined with ~~the F1CDx~~ a next-generation sequencing assay, and/or
wherein the cancer has been determined to have a TMB of ~~less than 400, less than 300 or~~ less than 200 missense mutations as determined by whole exome sequencing (WES), and
wherein the anti-CSF1R antibody is to be administered to the subject at a dose of ~~2, 3,~~ or 4 mg/kg once every two weeks and the anti-PD-1 antibody is to be administered to the subject at a dose of 400-600 mg once every four weeks,
wherein the anti-CSF1R antibody comprises a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 5, an HC CDR2 having the sequence of SEQ ID NO: 6, and an HC CDR3 having the sequence of SEQ ID NO: 7, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 8, a LC CDR2 having the sequence of SEQ ID NO: 9, and a LC CDR3 having the sequence of SEQ ID NO: 10; and
wherein the anti-PD-1 antibody comprises a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 28, an HC CDR2 having the sequence of SEQ ID NO: 30, and an HC CDR3 having the sequence of SEQ ID NO: 32, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 35, a LC CDR2 having the sequence of SEQ ID NO: 37, and a LC CDR3 having the sequence of SEQ ID NO: 39.
2. The use of claim 1, wherein the subject is to be administered gemcitabine or 5-fluorouracil (5-FU).
3. The use of claim 1 or 2, wherein the subject is to be administered 4 mg/kg of the anti-CSF1R antibody once every two weeks and 450-500 mg the anti-PD-1 antibody once every four weeks.
4. The use of claim 3, wherein the subject is to be administered 4 mg/kg of the anti-CSF1R antibody once every two weeks and 480 mg the anti-PD-1 antibody once every four weeks.
5. The use of any one of claims 1-4, wherein the subject is to be administered

chemotherapy comprising gemcitabine and nab-paclitaxel.

6. The use of any one of claims 1-4, wherein the subject is to be administered chemotherapy comprising 5-FU, leucovorin, and liposomal irinotecan.

7. The use of any one of claims 1-4, wherein the subject is to be administered chemotherapy comprising FOLFOX.

8. The use of any one of claims 1-7, wherein the anti-CSF1R antibody and/or the anti-PD-1 antibody is a Fab, an Fv, an scFv, a Fab', or a (Fab')₂ fragment.

9. The use of any one of claims 1-7, (a) wherein the anti-PD-1 antibody heavy chain comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 23 and wherein the anti-PD-1 antibody light chain comprises a light chain variable region comprising the sequence of SEQ ID NO: 25; (b) wherein the anti-PD-1 antibody comprises a heavy chain comprising the sequence of each of SEQ ID NOs: 23 and 24 and wherein the anti-PD-1 antibody comprises a light chain comprising the sequence of each of SEQ ID NOs: 25 and 26; or (c) wherein the anti-PD-1 antibody is nivolumab.

10. The use of any one of claims 1-7, (a) wherein the anti-CSF1R antibody comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 11 and wherein the anti-CSF1R antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 12; (b) wherein the anti-CSF1R antibody comprises a heavy chain comprising the sequence of SEQ ID NO: 13 and wherein the anti-CSF1R antibody comprises a light chain comprising the sequence of SEQ ID NO: 14; or (c) wherein the anti-CSF1R antibody is cabiralizumab.

11. The use of any one of claims 1-10, wherein the subject meets one or more of the following criteria:

- has previously failed treatment with a standard therapy for pancreatic cancer or is not indicated for treatment with a standard therapy;
- has previously received a PD-1/PD-L1 inhibitor therapy;
- is a PD-1/PD-L1 inhibitor inadequate responder;
- is refractory to a PD-1/PD-L1 inhibitor, e.g., after at least 2 doses;
- has a localized adenocarcinoma of the pancreas;
- has metastatic adenocarcinoma of the pancreas;
- does not have active pancreatitis or ascites of Grade 2 or higher;
- has a pancreatic tumor that is PD-L1 positive;

- has reduced circulating CD14⁺ CD16⁺⁺ nonclassical monocytes after at least one dose of each of the anti-CSF1R antibody and the anti-PD-1 antibody;
- has CD14⁺CD16⁺⁺ nonclassical monocytes that are reduced below 10 monocytes per microliter peripheral blood within 3 days after a first dose of each of the anti-CSF1R antibody and the anti-PD-1 antibody and that remain below 10 monocytes per microliter peripheral blood for at least 10 further days.

12. The use of any one of claims 1-11, wherein the subject has advanced pancreatic cancer.

13. The use of any one of claims 1-12, wherein the subject's pancreatic cancer has progressed after at least one gemcitabine-based or 5-fluorouracil-based chemotherapy regimen.

14. The use of any one of claims 1-13, wherein:

a) the expression level of at least one marker gene is to be determined both prior to and following the administration, the at least one marker gene comprising one or more of: CCL19, CCL5, CCL8, CCR7, CD86, CXCL10, CXCL11, CXCL13, CXCL9, IFNG, IL23A, STAT1, TNF, CD72, CD79A, CD79B, MS4A1, TNFRSF17, CD3D, CD8A, CD8B, GZMM, APOL3, CTSW, GNLY, GZMA, GZMH, KLRB1, KLRD1, KLRK1, NKG7, PRF1, BTLA, CD244, CD96, CTLA4, LAG3, PDCD1, TIGIT, and FOXP3; and

b) the anti-CSF1R antibody and anti-PD-1 antibody are continued to be administered to the subject if the expression level of the at least one marker gene increases following the administration of a) compared to the expression level determined prior to the administration of a).

15. The use of any one of claims 1-14 wherein:

a) the expression level of at least one marker gene is determined to increase following the administration, the at least one marker gene comprising one or more of: CCL19, CCL5, CCL8, CCR7, CD86, CXCL10, CXCL11, CXCL13, CXCL9, IFNG, IL23A, STAT1, TNF, CD72, CD79A, CD79B, MS4A1, TNFRSF17, CD3D, CD8A, CD8B, GZMM, APOL3, CTSW, GNLY, GZMA, GZMH, KLRB1, KLRD1, KLRK1, NKG7, PRF1, BTLA, CD244, CD96, CTLA4, LAG3, PDCD1, TIGIT, and FOXP3; and

b) the anti-CSF1R antibody and anti-PD-1 antibody are continued to be administered to the subject.

16. The use of any one of claims 1-15 wherein:

a) the expression level of at least one marker gene comprising one or both of CSF-1 and IL-34 is to be determined both prior to and following the administration; and

b) the anti-CSF1R antibody and anti-PD-1 antibody are continued to be administered to the subject if the expression level of the at least one marker gene comprising one or both of CSF-1 and IL-34 increases following the administration of a) compared to the expression level determined prior to administration of a).

17. The use of any one of claims 1-16 wherein: a) the expression level of at least one marker gene comprising one or both of CSF-1 and IL-34 is determined to increase following the administration, and b) the anti-CSF1R antibody and anti-PD-1 antibody are continued to be administered to the subject.