

inhibitory signals, or “immune checkpoints,” play an important role in normal tissues by preventing autoimmunity. Up-regulation of immune checkpoint proteins allows cancers to evade anti-tumor immunity. Two immune checkpoint proteins have been the focus of clinical cancer immunotherapeutics, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1). The combination of an anti-CTLA-4 antibody and an anti-PD-1 antibody has been approved for the treatment of metastatic melanoma and several additional clinical trials are also ongoing to study the use of this combination for the treatment of other cancers. Anti-PD-1 antibodies and anti-CTLA-4 antibodies for use as monotherapies are also currently being studied in clinical trials as a treatment for many different types of cancer. Anti-PD-L1 antibodies which bind PD-L1, one of the ligands for PD-1, are also currently in clinical development.

[005] Many tumors often express multiple checkpoint molecules simultaneously, Therefore, combinations of checkpoint modulators are undergoing clinical testing with aim of improved efficacy. Initial clinical results of the combination of an anti-CTLA-4 antibody (anti-CTLA-4 Ab) and an anti-PD-1 antibody (anti-PD-1 Ab) have demonstrated improved overall response rates, increased complete response rates, as well as overall survival rates in metastatic melanoma, compared to anti-CTLA-4 Ab alone or historical controls.

SUMMARY

[006] As described herein, Phase Ia/b studies of an anti-PD-1 antibody in combination with an anti-CSF1R antibody are ongoing. (*See, e.g.*, clinical trial NCT02526017, summary available at the Internet site [clinicaltrials \(dot\) gov.](http://clinicaltrials.gov)) Based on preliminary safety and pharmacodynamics, a particular dosage regime for a combination of cabiralizumab (anti-CSF1R antibody) and nivolumab (anti-PD-1 antibody) for pancreatic cancer patients has been selected for dose expansion studies.

[007] In some examples, this disclosure provides methods of treating cancer, such as solid tumors, e.g., pancreatic cancer, including pancreatic ductal adenocarcinoma, advanced pancreatic cancer, metatatic 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 4 mg/kg of an anti-CSF1R antibody and 3 mg/kg an anti-PD-1

antibody, wherein the antibodies are each administered once every two weeks, and 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 some examples, the anti-CSF1R antibody and/or the anti-PD-1 antibody comprises full length heavy and/or light chains, or alternatively, is a Fab, an Fv, an scFv, a Fab', or a (Fab')₂ fragment.

[008] 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.

[009] 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-CSF1R antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 12. In some examples, 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. In some examples, the anti-CSF1R antibody is cabiralizumab.

[010] In some examples, the anti-PD-1 antibody is administered to the subject before the anti-CSF1R antibody. In some such examples, the anti-CSF1R antibody is administered from 30 minutes to 120 minutes after the PD-1/PD-L1 inhibitor. In some examples, the anti-PD-1 antibody is infused over a period of 30-60 minutes, and the anti-

CSF1R antibody is infused over a period of 30-60 minutes. In some examples, the infusion of the anti-CSF1R antibody is initiated 30-120 minutes after the end of the infusion of the anti-PD-1 antibody. In some examples, the infusion of the anti-CSF1R antibody is initiated 30-60 minutes (e.g., 30 minutes) after the end of the infusion of the anti-PD-1 antibody.

[011] In some examples, the subject has previously failed treatment with a standard therapy for pancreatic cancer or is not indicated for treatment with a standard therapy. In some examples, the subject has previously received a PD-1/PD-L1 inhibitor therapy. In some such examples, the subject is a PD-1/PD-L1 inhibitor inadequate responder. In some examples, the subject is refractory to a PD-1/PD-L1 inhibitor, e.g., after at least 2 doses.

[012] In some examples, the subject has a localized adenocarcinoma of the pancreas. In some examples, the subject has metastatic adenocarcinoma of the pancreas. In some examples, the subject has advanced pancreatic cancer. In some examples, the subject does not have active pancreatitis or ascites of Grade 2 or higher. In some examples, the subject's pancreatic tumor(s) are PD-L1 positive. In some examples, the subject 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. For example, in some cases the CD14⁺CD16⁺⁺ nonclassical monocytes 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 remain below 10 monocytes per microliter peripheral blood for at least 10 further days. In some examples, the subject has advanced pancreatic cancer and/or metastatic pancreatic cancer, such as with metastasis to another organ such as liver and/or lung, and/or is a microsatellite-stable (MSS) subject and/or has a microsatellite-stable tumor. In some examples, the pancreatic cancer has been determined to be microsatellite-stable (MSS) and/or 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 by the Foundation One® CDx™ assay or less than 400, less than 300, or less than 200 missense mutations by WES. In some examples, the subject's pancreatic cancer has progressed after at least one gemcitabine-based or 5-fluorouracil-based chemotherapy regimen.

[013] Encompassed herein are also methods of treating cancer, such as solid tumors, e.g., pancreatic cancer, including pancreatic ductal adenocarcinoma, advanced pancreatic cancer,

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 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-

CSF1R antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 12. In some examples, 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. In some examples, the anti-CSF1R antibody is cabiralizumab. In some examples, the anti-PD-1 antibody is infused over a period of 30-60 minutes, and the anti-CSF1R antibody is infused over a period of 30-60 minutes. In some examples, the subject has previously failed treatment with a standard therapy for pancreatic cancer or is not indicated for treatment with a standard therapy.

[016] In some examples, the subject has previously received a PD-1/PD-L1 inhibitor therapy. In some such cases, the subject is a PD-1/PD-L1 inhibitor inadequate responder. In some such cases, the subject is refractory to a PD-1/PD-L1 inhibitor, e.g., after at least 2 doses. In some examples, the subject has a localized adenocarcinoma of the pancreas. In some examples, the subject has metastatic adenocarcinoma of the pancreas. In some examples, the subject does not have active pancreatitis or ascites of Grade 2 or higher. In some examples, the subject's pancreatic tumor(s) are PD-L1 positive. In some examples, the subject 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. In some examples, the CD14⁺CD16⁺⁺ nonclassical monocytes 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 remain below 10 monocytes per microliter peripheral blood for at least 10 further days. In some examples, subject has advanced pancreatic cancer and/or metastatic pancreatic cancer, such as with metastasis to another organ such as liver and/or lung, and/or is a microsatellite-stable (MSS) subject. In some examples, the pancreatic cancer has been determined to be microsatellite-stable (MSS) and/or 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 by the Foundation One® CDx™ assay or less than 400, less than 300, or less than 200 missense mutations by WES. In some examples, the subject's pancreatic cancer has progressed after at least one gemcitabine-based or 5-fluorouracil-based chemotherapy regimen.

[017] Encompassed herein are also methods of treating cancer, such as solid tumors, e.g., pancreatic cancer, including pancreatic ductal adenocarcinoma, advanced pancreatic cancer, 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 in combination with chemotherapy comprising gemcitabine or 5-fluorouracil (5-FU), 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 and chemotherapy comprising gemcitabine or 5-fluorouracil (5-FU) for preparation of a medicament for treatment of pancreatic cancer in a subject, 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.

[018] 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. In some examples, the subject is administered chemotherapy comprising gemcitabine and nab-paclitaxel. In some examples, the subject is administered chemotherapy comprising 5-FU, leucovorin, and liposomal irinotecan. In some examples, the subject is administered chemotherapy comprising FOLFOX. In some examples, the anti-CSF1R antibody comprises full length heavy and/or light chains, or alternatively, 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 alternatively, is a Fab, an Fv, an scFv, a Fab', or a (Fab')₂ fragment.

[019] 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-CSF1R antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 12. In some examples, 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. In some examples, the anti-CSF1R antibody is cabiralizumab. In some examples, the anti-PD-1 antibody is infused over a period of 30-60 minutes, and the anti-CSF1R antibody is infused over a period of 30-60 minutes.

[020] In some examples, the subject has previously failed treatment with a standard therapy for pancreatic cancer or is not indicated for treatment with a standard therapy. In some examples, the subject has previously received a PD-1/PD-L1 inhibitor therapy. In some examples, the subject is a PD-1/PD-L1 inhibitor inadequate responder.

[021] In some examples, the subject is refractory to a PD-1/PD-L1 inhibitor, e.g., after at least 2 doses. In some examples, the subject has a localized adenocarcinoma of the pancreas. In some examples, the subject has metastatic adenocarcinoma of the pancreas. In some examples, the subject does not have active pancreatitis or ascites of Grade 2 or higher. In some examples, the subject's pancreatic tumor(s) are PD-L1 positive. In some examples, subject 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. In some examples, the CD14⁺CD16⁺⁺ nonclassical monocytes 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 remain below 10 monocytes per microliter peripheral blood for at least 10 further days. In some examples, subject has advanced pancreatic cancer and/or metastatic pancreatic cancer, such as with metastasis to another organ such as liver and/or lung, and/or is a microsatellite-stable (MSS) subject. In some examples, the pancreatic cancer has

been determined to be microsatellite-stable (MSS) and/or 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 by the Foundation One® CDx™ assay, and/or less than 400, less than 300, or less than 200 missense mutations, as determined by whole exome sequencing (WES). In some examples, the subject's pancreatic cancer has progressed after at least one gemcitabine-based or 5-fluorouracil-based chemotherapy regimen.

[022] The disclosure herein also encompasses methods of treating cancer in a subject comprising administering to the subject an anti-CSF1R antibody and an anti-PD-1 antibody, wherein the cancer has been determined to be microsatellite-stable (MSS) and/or has been determined to have a TMB of less than 20, 15 or 10 mutations/megabase, as determined by the Foundation One® CDx™ assay, and/or less than 400, less than 300, or less than 200 missense mutations, as determined by WES. 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 cancer in a subject, wherein the cancer has been determined to be microsatellite-stable (MSS) and/or has been determined to have a TMB of less than 20, less than 15 or less than 10 mutations/megabase, as determined with the F1CDx 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 WES. In some examples, the cancer has been determined (i) to be MSS and (ii) to have a TMB of less than 20, 15 or 10 mutations/megabase, as determined by the Foundation One® CDx™ assay, and/or less than 400, 300, or 200 missense mutations, as determined by WES. In some examples, the cancer has been determined to have a TMB of less than 15 mutations/megabase, as determined by the Foundation One® CDx™ assay, and/or less than 300 missense mutations, as determined by WES. In some examples, the cancer has been determined to have a TMB of less than 10 mutations/megabase, as determined by the Foundation One® CDx™ assay, and/or less than 200 missense mutations, as determined by WES. In some such methods, 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 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 some methods, the anti-CSF1R antibody is a Fab, an Fv, an scFv, a Fab', or a (Fab')₂ fragment and/or the anti-PD-1

antibody is a Fab, an Fv, an scFv, a Fab', or a (Fab')₂ fragment. In some such methods, 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 or 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-CSF1R antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 12. In some examples, 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. In some examples, the anti-CSF1R antibody is cabiralizumab. In some examples, the anti-CSF-1R antibody is emactuzumab (RG7155), AMG 820, or SNDX 6352 (UCB 6352). In some examples, a non-antibody anti-CSF-1R agent is used in place of the anti-CSF1R antibody, such as a small molecule, e.g., JNJ-40346527 (now PRV-6527), e.g., an anti-CSF1R tyrosine kinase inhibitor, or other modality.

[023] In some of the above methods, the anti-PD-1 antibody is administered to the subject before the anti-CSF1R antibody. In some examples, the anti-CSF1R antibody is administered from 30 minutes to 120 minutes after the anti-PD-1 antibody. In some examples, the anti-PD-1 antibody is infused over a period of 30-60 minutes, and the anti-CSF1R antibody is infused over a period of 30-60 minutes. In some examples, the infusion of the anti-CSF1R antibody is initiated 30-120 minutes after the end of the infusion of the anti-PD-1 antibody. In some examples, the infusion of the anti-CSF1R antibody is initiated 30-60 minutes (e.g., 30 minutes) after the end of the infusion of the anti-PD-1 antibody. In some examples, the subject has previously received a PD-1/PD-L1 inhibitor therapy. In some embodiments, the subject is a PD-1/PD-L1 inhibitor inadequate responder. In some examples, the subject is refractory to a PD-1/PD-L1 inhibitor, e.g., after at least 2 doses. In some examples, the anti-CSF1R antibody is cabiralizumab and the anti-PD-1 antibody is nivolumab, wherein cabiralizumab is administered at a dose of 4 mg/kg once every two weeks,

and wherein nivolumab is administered at a dose of 3 mg/kg once every two weeks. In some examples, the cancer is pancreatic cancer, ovarian cancer, renal cancer, malignant glioma, melanoma, non-small cell lung cancer (NSCLC), or squamous cell carcinoma of the head and neck (SCCHN).

[024] The disclosure herein also contemplates methods of treating cancer in a subject, comprising administering to the subject at least one dose of an anti-CSF1R antibody and an anti-PD-1 antibody, such as, for example a single dose or two doses of the antibodies, wherein the expression level of at least one marker gene is 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. If the expression level data indicates that the expression level of the at least one marker gene increases following the administration, administration of the anti-CSF1R antibody and anti-PD-1 antibody to the subject may then continue. 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 cancer in a subject, wherein: a) at least one dose of the anti-CSF1R antibody and the anti-PD-1 antibody is to be administered to the subject, wherein 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). Some examples comprise a method of treating cancer in a subject, comprising administering to the subject at least one dose of an anti-CSF1R antibody and an anti-PD-1 antibody, wherein 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 then continuing to administer the anti-CSF1R antibody and anti-PD-1 antibody to the subject. 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 cancer in a subject, wherein: a) at least one dose of an anti-CSF1R antibody and an anti-PD-1 antibody is to be administered to the subject, wherein 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. In further examples, the method comprises first determining or having determined the expression level of 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, then administering at least one dose of the anti-CSF1R antibody and the anti-PD-1 antibody, such as

one or two doses of the antibodies, and then re-determining or having determined the expression level of the at least one marker gene. If the expression level data indicates that the expression level of the at least one marker gene increases following the administration, administration of the anti-CSF1R antibody and anti-PD-1 antibody to the subject may then continue. In yet further examples, the method comprises first determining or having determined the expression level of 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, then administering at least one dose of the anti-CSF1R antibody and the anti-PD-1 antibody, such as one or two doses of the antibodies, and then determining that the expression level of the at least one marker gene has increased following the administration, followed by further administration of the anti-CSF1R antibody and anti-PD-1 antibody to the subject. Examples herein also include methods of treating cancer in a subject, comprising administering to the subject at least one dose of an anti-CSF1R antibody and an anti-PD-1 antibody, wherein the expression level of at least one marker gene comprising one or both of CSF-1 and IL-34 is determined both prior to and following the administration; and continuing to administer the anti-CSF1R antibody and anti-PD-1 antibody 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. 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 cancer in a subject, wherein: a) at least one dose of an anti-CSF1R antibody and an anti-PD-1 antibody is to be administered to the subject, wherein 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). Examples herein also include methods of treating cancer in a subject, comprising administering to the subject at least one dose of an anti-CSF1R antibody and an anti-PD-1 antibody, wherein 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 continuing to administer the anti-CSF1R antibody and anti-PD-1 antibody to the subject. 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 cancer in a subject, wherein: a) at least one dose of an anti-CSF1R antibody and an anti-PD-1 antibody are to be administered to the subject, wherein 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. Examples herein also include methods of treating cancer in a subject, comprising administering to the subject at least one dose of an anti-CSF1R antibody and an anti-PD-1 antibody, determining the expression level of at least one marker gene comprising one or both of CSF-1 and IL-34 both prior to and after the administration, wherein, if the expression level of the at least one marker gene is determined to increase following the administration, then continuing to administer the anti-

CSF1R antibody and anti-PD-1 antibody to the subject. Examples herein also include methods of treating cancer in a subject, comprising administering to the subject at least one dose of an anti-CSF1R antibody and an anti-PD-1 antibody, determining that the expression level of at least one marker gene comprising one or both of CSF-1 and IL-34 has increased after the administration, then continuing to administer the anti-CSF1R antibody and anti-PD-1 antibody to the subject.

[025] In any of the above methods, the at least one marker gene comprises: (a) at least one pro-inflammatory marker gene comprising: CCL19, CCL5, CCL8, CCR7, CD86, CXCL10, CXCL11, CXCL13, CXCL9, IFNG, IL23A, STAT1, and TNF, (b) at least one B cell marker comprising: CD72, CD79A, CD79B, MS4A1, and TNFRSF17, (c) at least one CD8 T cell marker comprising: CD3D, CD8A, and CD8B, (d) at least one effector T cell cytolytic marker comprising: GZMM, APOL3, CTSW, GNLY, GZMA, GZMH, KLRB1, KLRD1, KLRK1, NKG7, and PRF1; and/or (e) at least one effector T cell receptor marker comprising: BTLA, CD244, CD96, CTLA4, LAG3, PDCD1, TIGIT, and FOXP3. Any of the above methods may further comprise measuring the expression level of one or more of CSF1R, CSF-1 and IL-34, wherein increases in CSF-1 and IL-34 expression levels following administration indicate that the subject is responsive to treatment with the anti-CSF1R antibody and anti-PD-1 antibody while a decrease in CSF1R expression level indicates that the subject is not responsive to treatment with the anti-CSF1R antibody and anti-PD-1 antibody. In some examples, the methods further comprise determining the expression level of one or more anti-inflammatory markers comprising: ARG1, C5AR1, CD14, CD163, CXCR1, CXCR2, IL1A, IL1RN, IL8, MRC1, MSR1, PF4, PPBP, S100A12, S100A8, SAA1, S100A9, and TGFB1. In some examples, the levels of these markers do not change or do not increase in subjects responsive to treatment with the anti-CSF1R antibody and the anti-PD-1 antibody.

[026] In any of the above methods, the expression level of the at least one marker gene may be the RNA expression level, e.g., measured by transcriptome analysis or reverse transcription PCR. In any of the above methods, the expression level may, for instance, be measured in tumor cells, i.e., in cells from a tumor sample such as a biopsy sample. In any of the above cancer treatment methods, the cancer may have been determined to be MSS and/or has been determined to have a TMB of less than 20, less than 15 or less than 10 mutations/megabase,

as determined by the Foundation One® CDx™ assay, and/or less than 400, less than 300, or less than 200 missense mutations, as determined by whole exome sequencing (WES). In some examples, the cancer has been determined (i) to be MSS and (ii) to have a TMB of less than 20, less than 15 or less than 10 mutations/megabase, as determined by the Foundation One® CDx™ assay, and/or less than 400, less than 300, or less than 200 missense mutations, as determined by WES. In some examples, the cancer has been determined to have a TMB of less than 15 mutations/megabase, as determined by the Foundation One® CDx™ assay, and/or less than 300 missense mutations, as determined by WES. In some embodiments, the cancer has been determined to have a TMB of less than 10 mutations/megabase, as determined by the Foundation One® CDx™ assay, and/or less than 200 missense mutations, as determined by WES.

[027] In some embodiments, the anti-CSF1R antibody may comprise 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 the anti-PD-1 antibody may comprise 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 some examples, the anti-CSF1R antibody is a Fab, an Fv, an scFv, a Fab', or a (Fab')₂ fragment. In some examples, the anti-PD-1 antibody 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 or 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-CSF1R antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 12. In some examples, 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. In some examples, the anti-CSF1R antibody is cabiralizumab. In some examples, the anti-PD-1 antibody is administered to the subject before the anti-CSF1R antibody. In some examples, the anti-CSF1R antibody is administered from 30 minutes to 120 minutes after the anti-PD-1 antibody. In some examples, the anti-PD-1 antibody is infused over a period of 30-60 minutes, and the anti-CSF1R antibody is infused over a period of 30-60 minutes. In some examples, the infusion of the anti-CSF1R antibody is initiated 30-120 minutes after the end of the infusion of the anti-PD-1 antibody. In some examples, the infusion of the anti-CSF1R antibody is initiated 30-60 minutes (e.g., 30 minutes) after the end of the infusion of the anti-PD-1 antibody. In some examples, the subject has previously received a PD-1/PD-L1 inhibitor therapy. In some examples, the subject is a PD-1/PD-L1 inhibitor inadequate responder. In some examples, the subject is refractory to a PD-1/PD-L1 inhibitor, e.g., after at least 2 doses. In some examples, the anti-CSF1R antibody is cabiralizumab and the anti-PD-1 antibody is nivolumab, wherein cabiralizumab is administered at a dose of 4 mg/kg once every two weeks, and wherein nivolumab is administered at a dose of 3 mg/kg once every two weeks. In some examples, the cancer is pancreatic cancer, ovarian cancer, renal cancer, malignant glioma, melanoma, non-small cell lung cancer (NSCLC), or squamous cell carcinoma of the head and neck (SCCHN). In some examples, the anti-CSF-1R antibody is emactuzumab (RG7155), AMG 820, or SNDX 6352 (UCB 6352). In some examples, a non-antibody CSF-1R inhibitor is used in place of the anti-CSF1R antibody, such as a small molecule, e.g., JNJ-40346527 (now PRV-6527), e.g., an anti-CSF1R tyrosine kinase inhibitor, or other modality.

[028] The present disclosure also includes a method of determining responsiveness of a subject with cancer to treatment with a combination of an anti-CSF1R antibody and an anti-PD-1 antibody, the method comprising determining the expression level of at least one marker gene before and after the subject is administered at least one dose of the anti-CSF1R antibody and the

anti-PD-1 antibody, 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. A increase in the expression level of the at least one marker gene indicates responsiveness in some examples. In one aspect, the present disclosure refers to a method of determining responsiveness of a subject with cancer to treatment with a combination of an anti-CSF1R antibody and an anti-PD-1 antibody, the method comprising determining the expression level of at least one marker gene in a sample from the subject before and after the subject is administered at least one dose of the anti-CSF1R antibody and the anti-PD-1 antibody, 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, wherein an increase in the expression level of the at least one marker gene following administration indicates that the subject is responsive to treatment with the combination of the anti-CSF1R antibody and the anti-PD-1 antibody. In any of the above methods, the at least one marker gene comprises: (a) at least one pro-inflammatory marker gene comprising: CCL19, CCL5, CCL8, CCR7, CD86, CXCL10, CXCL11, CXCL13, CXCL9, IFNG, IL23A, STAT1, and TNF, (b) at least one B cell marker comprising: CD72, CD79A, CD79B, MS4A1, and TNFRSF17, (c) at least one CD8 T cell marker comprising: CD3D, CD8A, and CD8B, (d) at least one effector T cell cytolytic marker comprising: GZMM, APOL3, CTSW, GNLY, GZMA, GZMH, KLRB1, KLRD1, KLRK1, NKG7, and PRF1; and/or (e) at least one effector T cell receptor marker comprising: BTLA, CD244, CD96, CTLA4, LAG3, PDCD1, TIGIT, and FOXP3. Any of the above methods may further comprise measuring the expression level of one or more of CSF1R, CSF-1 and IL-34, wherein increases in CSF-1 and IL-34 expression levels following administration indicate that the subject is responsive to treatment with the anti-CSF1R antibody and anti-PD-1 antibody while a decrease in CSF1R expression level indicates that the subject is not responsive to treatment with the anti-CSF1R antibody and anti-PD-1 antibody. Also included herein are methods of determining responsiveness of a subject with cancer to treatment with a combination of an anti-CSF1R antibody and an anti-PD-1 antibody, the method comprising determining the expression level of at least one marker gene before and after the subject is administered at least one dose of the anti-CSF1R antibody and the anti-PD-1 antibody, the at least one marker gene comprising one or both of CSF-1 and IL-34, wherein an increase in the expression level of the at least one marker gene following administration indicates that the subject is responsive to treatment with the combination of the anti-CSF1R antibody and the anti-PD-1 antibody. In one aspect, the present disclosure refers to a method of determining responsiveness of a subject with cancer to treatment with a combination of an anti-CSF1R antibody and an anti-PD-1 antibody, the method comprising determining the expression level of at least one marker gene in a sample from the subject before and after the subject is administered at least one dose of the anti-CSF1R antibody and the anti-PD-1 antibody, the at least one marker gene comprising one or both of CSF-1 and IL-34, wherein an increase in the expression level of the at least one marker gene following administration indicates that the subject is responsive to treatment with the combination of the anti-CSF1R antibody and the anti-PD-1 antibody.

[029] In some examples, the methods further comprise determining the expression level of one or more anti-inflammatory markers comprising: ARG1, C5AR1, CD14, CD163, CXCR1, CXCR2, IL1A, IL1RN, IL8, MRC1, MSR1, PF4, PPBP, S100A12, S100A8, SAA1, S100A9, and TGFB1. In some examples, the levels of these markers do not change or do not

increase in subjects responsive to treatment with the anti-CSF1R antibody and the anti-PD-1 antibody. In some examples, the subject is administered one or two doses of the anti-CSF1R antibody and anti-PD-1 antibody between determinations of the expression level of the at least one marker gene. In some examples, the methods further comprise determining the expression level of one or more anti-inflammatory markers comprising: ARG1, C5AR1, CD14, CD163, CXCR1, CXCR2, IL1A, IL1RN, IL8, MRC1, MSR1, PF4, PPBP, S100A12, S100A8, SAA1, S100A9, and TGFB1. In some examples, the levels of these markers do not change or do not increase in subjects responsive to treatment with the anti-CSF1R antibody and the anti-PD-1 antibody. In any of the above methods, the expression level of the at least one marker gene may be the RNA expression level, e.g., measured by transcriptome analysis or reverse transcription PCR. In any of the above methods, the expression level may, for instance, be measured in tumor cells, i.e., in cells from a tumor sample such as a biopsy sample. In any of the above methods, the cancer may have been determined to be MSS and/or has been determined to have a TMB of less than 20, less than 15 or less than 10 mutations/megabase, as determined by the Foundation One® CDx™ assay, and/or less than 400, less than 300, or less than 200 missense mutations, as determined by WES. In some examples, the cancer has been determined (i) to be MSS and (ii) to have a TMB of less than 20, less than 15 or less than 10 mutations/megabase, as determined by the Foundation One® CDx™ assay, and/or less than 400, less than 300, or less than 200 missense mutations, as determined by WES. In some examples, the cancer has been determined to have a TMB of less than 15 mutations/megabase, as determined by the Foundation One® CDx™ assay, and/or less than 300 mutations/megabase, as determined by WES. In some embodiments, the cancer has been determined to have a TMB of less than 10 mutations/megabase, as determined by the Foundation One® CDx™ assay, and/or less than 200 missense mutations, as determined by WES.

[030] In some embodiments, the anti-CSF1R antibody may comprise 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 the anti-PD-1 antibody may comprise 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 some examples, the anti-CSF1R antibody is a Fab, an Fv, an scFv, a Fab', or a (Fab')₂ fragment. In some examples, the anti-PD-1 antibody 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 or 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-CSF1R antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 12. In some examples, 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. In some examples, the anti-CSF1R antibody is cabiralizumab. In some examples, the anti-CSF-1R antibody is emactuzumab (RG7155), AMG 820, or SNDX 6352 (UCB 6352). In some examples, a non-antibody CSF1R inhibitor is used in place of the anti-CSF1R antibody, such as a small molecule, e.g., JNJ-40346527 (now PRV-6527), e.g., an anti-CSF1R tyrosine kinase inhibitor, or other modality.

[031] In some examples, the subject has previously received a PD-1/PD-L1 inhibitor therapy. In some examples, the subject is a PD-1/PD-L1 inhibitor inadequate responder. In some examples, the subject is refractory to a PD-1/PD-L1 inhibitor, e.g., after at least 2 doses. In some examples, the anti-CSF1R antibody is cabiralizumab and the anti-PD-1 antibody is nivolumab, wherein cabiralizumab is administered at a dose of 4 mg/kg once every two weeks, and wherein nivolumab is administered at a dose of 3 mg/kg once every two weeks. In some examples, the cancer is pancreatic cancer, ovarian cancer, renal cancer,

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 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. Use of an anti-CSF1R antibody and an anti-PD-1 antibody and chemotherapy comprising gemcitabine or 5-fluorouracil (5-FU) for preparation of a medicament for treatment of pancreatic cancer in a subject, 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.

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 cancer has been determined to be microsatellite-stable (MSS) and/or 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 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 WES.

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

15. Use of an anti-CSF1R antibody and an anti-PD-1 antibody for preparation of a medicament for treatment of cancer in a subject, wherein the cancer has been determined to be microsatellite-stable (MSS) and/or has been determined to have a TMB of less than 20, less than 15 or less than 10 mutations/megabase, as determined with the F1CDx 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 WES.

16. Use of an anti-CSF1R antibody and an anti-PD-1 antibody for preparation of a medicament for treatment of cancer in a subject, wherein:

a) at least one dose of the anti-CSF1R antibody and the anti-PD-1 antibody is to be administered to the subject, wherein 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).

17. Use of an anti-CSF1R antibody and an anti-PD-1 antibody for preparation of a medicament for treatment of cancer in a subject, wherein:

a) at least one dose of an anti-CSF1R antibody and an anti-PD-1 antibody is to be administered to the subject, wherein 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.

18. Use of an anti-CSF1R antibody and an anti-PD-1 antibody for preparation of a medicament for treatment of cancer in a subject, wherein:

a) at least one dose of an anti-CSF1R antibody and an anti-PD-1 antibody is to be administered to the subject, wherein 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).

19. Use of an anti-CSF1R antibody and an anti-PD-1 antibody for preparation of a medicament for treatment of cancer in a subject, wherein: a) at least one dose of an anti-CSF1R antibody and an anti-PD-1 antibody are to be administered to the subject, wherein 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.

20. A method of determining responsiveness of a subject with cancer to treatment with a combination of an anti-CSF1R antibody and an anti-PD-1 antibody, the method comprising determining the expression level of at least one marker gene in a sample from the subject before and after the subject is administered at least one dose of the anti-CSF1R antibody and the anti-PD-1 antibody, 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, wherein an increase in the expression level of the at least one marker gene following administration indicates that the subject is responsive to treatment with the combination of the anti-CSF1R antibody and the anti-PD-1 antibody.

21. The method of claim 20, wherein the at least one marker gene comprises:
- a. at least one pro-inflammatory marker gene comprising: CCL19, CCL5, CCL8, CCR7, CD86, CXCL10, CXCL11, CXCL13, CXCL9, IFNG, IL23A, STAT1, and TNF;
 - b. at least one B cell marker comprising: CD72, CD79A, CD79B, MS4A1, and TNFRSF17;
 - c. at least one CD8 T cell marker comprising: CD3D, CD8A, and CD8B;
 - d. at least one effector T cell cytolytic marker comprising: GZMM, APOL3, CTSW, GNLY, GZMA, GZMH, KLRB1, KLRD1, KLRK1, NKG7, and PRF1; and/or
 - e. at least one effector T cell receptor marker comprising: BTLA, CD244, CD96, CTLA4, LAG3, PDCD1, TIGIT, and FOXP3.

22. A method of determining responsiveness of a subject with cancer to treatment

with a combination of an anti-CSF1R antibody and an anti-PD-1 antibody, the method comprising determining the expression level of at least one marker gene in a sample from the subject before and after the subject is administered at least one dose of the anti-CSF1R antibody and the anti-PD-1 antibody, the at least one marker gene comprising one or both of CSF-1 and IL-34, wherein an increase in the expression level of the at least one marker gene following administration indicates that the subject is responsive to treatment with the combination of the anti-CSF1R antibody and the anti-PD-1 antibody.