

responses, which are regulated by a balance between activating and inhibitory signals. The 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.

[006] 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.

[007] As described herein, significant antitumor activity of an anti-PD-1 antibody in combination with an anti-CSF1R antibody has been demonstrated in clinical trials.

SUMMARY

[007a] In one aspect, there is provided 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 anti-CSF1R antibody and anti-PD-1 antibody are to be administered concurrently or sequentially to the subject; and wherein:

the anti-CSF1R antibody is selected from:

a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 39 and a light chain comprising the sequence of SEQ ID NO: 46;

b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16, and an HC CDR3 having the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; and

c) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 53 and a light chain comprising the sequence of SEQ ID NO: 60, and

the anti-PD-1 antibody is selected from:

a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 100 and a light chain comprising the sequence of SEQ ID NO: 102;

b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 105, an HC CDR2 having the sequence of SEQ ID NO: 107, and an HC CDR3 having the sequence of SEQ ID NO: 109, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 112, a LC CDR2 having the sequence of SEQ ID NO: 114, and a LC CDR3 having the sequence of SEQ ID NO: 116; and

c) an antibody comprising a heavy chain comprising the sequences of SEQ ID NOs: 100 and 101 and a light chain comprising the sequences of SEQ ID NOs: 102 and 103.

[008] In some embodiments, methods of treating cancer in a subject are provided, comprising administering to the subject an anti-CSF1R antibody and a PD-1/PD-L1 inhibitor. In some embodiments, the PD-1/PD-L1 inhibitor is an antibody. In some embodiments, the PD-1/PD-L1 inhibitor is an anti-PD-1 antibody. In some embodiments, the anti-PD-1 antibody comprises the heavy chain and light chain CDRs of an antibody selected from nivolumab and pembrolizumab. In some embodiments, the anti-PD-1 antibody comprises the heavy chain and light chain variable regions of an antibody selected from nivolumab and pembrolizumab. In some embodiments, the anti-PD-1 antibody is selected from nivolumab and pembrolizumab. In some embodiments, the PD-1/PD-L1 inhibitor is an anti-PD-L1 antibody. In some embodiments, the anti-PD-L1 antibody comprises the heavy chain and light chain CDRs of an antibody selected from BMS-936559, MPDL3280A, MEDI4736, and MSB0010718C. In some embodiments, the anti-PD-L1 antibody comprises the heavy chain and light chain variable regions of an antibody selected from BMS-936559, MPDL3280A,

compared in a mouse xenograft model for the cancer compared to administration of the anti-CSF1R antibody or PD-1/PD-L1 inhibitor alone.

[015] In some embodiments of the uses and methods a patient with non-small cell lung cancer (NSCLC) is treated with the anti-CSF1R antibody (for instance, an anti-CSF1R antibody as described herein, such as an antibody comprising the heavy and light chain CDRs of HuAB1) and the PD-1/PD-L1 inhibitor (for instance, an anti-PD-1 antibody comprising the heavy chain and light chain CDRs of nivolumab or pembrolizumab or a PD-1/PD-L1 inhibitor fusion protein or peptide such as AMP-224 or AUR-012). In some such embodiments, the patient has Stage IIIB or IV disease and/or has demonstrated disease progression or recurrence during and/or after a platinum doublet-based or other chemotherapy regimen for advanced or metastatic disease. In some embodiments, the patient has not had prior exposure to a PD-1/PD-L1 inhibitor; and in other embodiments, the patient is refractory to PD-1/PD-L1 inhibitor treatment. In some embodiments, the anti-CSF1R antibody is administered at a dose of about 0.1, about 0.3, about 0.5, about 1, about 2, about 3, about 4, about 5 or about 10 mg/kg. In some embodiments, the PD-1/PD-L1 inhibitor is administered at a dose of 0.1-10 mg/kg, such as, for example about 0.1, about 0.3, about 0.5, about 1, about 2, about 3, about 4, about 5 or about 10 mg/kg mg/kg. In some embodiments, the anti-CSF1R antibody and the PD-1/PD-L1 inhibitor are administered, for example at one of the above doses, once per 1, 2, 3, 4, or 5 weeks, such as about once every 2 weeks. In some embodiments, administration of the anti-CSF1R antibody and the PD-1/PD-L1 inhibitor results in a synergistic effect on tumor growth, weight, and/or volume compared in a mouse xenograft model for NSCLC compared to administration of the anti-CSF1R antibody or PD-1/PD-L1 inhibitor alone.

[016] In some embodiments of the uses and methods, melanoma is treated with the anti-CSF1R antibody (for instance, an anti-CSF1R antibody as described herein, such as an antibody comprising the heavy and light chain CDRs of HuAB1) and the PD-1/PD-L1 inhibitor (for instance, an anti-PD-1 antibody comprising the heavy chain and light chain CDRs of nivolumab or pembrolizumab or a PD-1/PD-L1 inhibitor fusion protein or peptide such as AMP-224 or AUR-012). In some such embodiments, the patient has Stage III or IV melanoma. In some embodiments, the patient has demonstrated disease progression during or after treatment with at least one BRAF inhibitor, or is BRAF wild-type. In some embodiments, the patient has not had prior exposure to a PD-1/PD-L1 inhibitor, and in other embodiments, the patient is refractory to PD-1/PD-L1 inhibitor treatment. In some embodiments, the anti-CSF1R antibody is administered at a dose of about 0.1, about 0.3,

about 0.5, about 1, about 2, about 3, about 4, about 5 or about 10 mg/kg. In some embodiments, the PD-1/PD-L1 inhibitor is administered at a dose of 0.1-10 mg/kg, such as, for example about 0.1, about 0.3, about 0.5, about 1, about 2, about 3, about 4, about 5 or about 10 mg/kg mg/kg. In some embodiments, the anti-CSF1R antibody and the PD-1/PD-L1 inhibitor are administered, for example at one of the above doses, once per 1, 2, 3, 4, or 5 weeks, such as about once every 2 weeks. In some embodiments, administration of the anti-CSF1R antibody and the PD-1/PD-L1 inhibitor results in a synergistic effect on tumor growth, weight, and/or volume compared in a mouse xenograft model for melanoma compared to administration of the anti-CSF1R antibody or PD-1/PD-L1 inhibitor alone.

[017] In some embodiments of the uses and methods, squamous cell carcinoma of the head and neck (SSCHN) is treated with the anti-CSF1R antibody (for instance, an anti-CSF1R antibody as described herein, such as an antibody comprising the heavy and light chain CDRs of HuAB1) and the PD-1/PD-L1 inhibitor (for instance, an anti-PD-1 antibody comprising the heavy chain and light chain CDRs of nivolumab or pembrolizumab or a PD-1/PD-L1 inhibitor fusion protein or peptide such as AMP-224 or AUR-012). In some embodiments, the patient has Stage III or IV SSCHN or has recurrent or metastatic SSCHN. In some embodiments, the patient has previously received chemotherapy, such as platinum therapy, but has demonstrated tumor progression or recurrence. In some embodiments, the patient has previously received radiation therapy, optionally along with platinum therapy, but has demonstrated tumor progression or recurrence. In some embodiments, the patient has not had prior exposure to a PD-1/PD-L1 inhibitor, and in other embodiments, the patient is refractory to PD-1/PD-L1 inhibitor treatment. In some embodiments, the anti-CSF1R antibody is administered at a dose of about 0.1, about 0.3, about 0.5, about 1, about 2, about 3, about 4, about 5 or about 10 mg/kg. In some embodiments, the PD-1/PD-L1 inhibitor is administered at a dose of 0.1-10 mg/kg, such as, for example about 0.1, about 0.3, about 0.5, about 1, about 2, about 3, about 4, about 5 or about 10 mg/kg mg/kg. In some embodiments, the anti-CSF1R antibody and the PD-1/PD-L1 inhibitor are administered, for example at one of the above doses, once per 1, 2, 3, 4, or 5 weeks, such as about once every 2 weeks. In some embodiments, administration of the anti-CSF1R antibody and the PD-1/PD-L1 inhibitor results in a synergistic effect on tumor growth, weight, and/or volume compared in a mouse xenograft model for squamous cell carcinoma compared to administration of the anti-CSF1R antibody or PD-1/PD-L1 inhibitor alone.

[018] In some embodiments of the uses and methods, pancreatic cancer is treated with the anti-CSF1R antibody (for instance, an anti-CSF1R antibody as described herein, such as an

antibody comprising the heavy and light chain CDRs of HuAB1) and the PD-1/PD-L1 inhibitor (for instance, an anti-PD-1 antibody comprising the heavy chain and light chain CDRs of nivolumab or pembrolizumab or a PD-1/PD-L1 inhibitor fusion protein or peptide such as AMP-224 or AUR-012). In some embodiments, the patient has documented localized or metastatic adenocarcinoma of the pancreas. In some embodiments, the patient may previously have received surgery and/or radiation therapy. In some embodiments, the patient has not had prior exposure to a PD-1/PD-L1 inhibitor, and in other embodiments, the patient is refractory to PD-1/PD-L1 inhibitor treatment. In some embodiments, the anti-CSF1R antibody is administered at a dose of 0.1, 0.3, 1, 2, 3, or 4 mg/kg. In some embodiments, the PD-1/PD-L1 inhibitor is administered at a dose of 0.5-10 mg/kg, such as, for example 1, 2, 3, 4, or 5 mg/kg. In some embodiments, the anti-CSF1R antibody and the PD-1/PD-L1 inhibitor are administered, for example at one of the above doses, once per 1, 2, 3, 4, or 5 weeks, such as once every 2 weeks. In some embodiments of the uses and methods, colorectal cancer is treated with the anti-CSF1R antibody (for instance, an anti-CSF1R antibody as described herein, such as an antibody comprising the heavy and light chain CDRs of HuAB1) and the PD-1/PD-L1 inhibitor (for instance, an anti-PD-1 antibody comprising the heavy chain and light chain CDRs of nivolumab or pembrolizumab or a PD-1/PD-L1 inhibitor fusion protein or peptide such as AMP-224 or AUR-012). In some embodiments, the patient has adenocarcinoma of the colon or rectum. In some embodiments, the patient has metastatic colorectal cancer. In some embodiments, the patient has metastatic colorectal cancer despite prior treatment with one or more of fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, cetuximab, or panitumumab. In some embodiments, the patient has not had prior exposure to a PD-1/PD-L1 inhibitor, and in other embodiments, the patient is refractory to PD-1/PD-L1 inhibitor treatment. In some embodiments, the anti-CSF1R antibody is administered at a dose of about 0.1, about 0.3, about 0.5, about 1, about 2, about 3, about 4, about 5 or about 10 mg/kg. In some embodiments, the PD-1/PD-L1 inhibitor is administered at a dose of 0.1-10 mg/kg, such as, for example about 0.1, about 0.3, about 0.5, about 1, about 2, about 3, about 4, about 5 or about 10 mg/kg mg/kg. In some embodiments, the anti-CSF1R antibody and the PD-1/PD-L1 inhibitor are administered, for example at one of the above doses, once per 1, 2, 3, 4, or 5 weeks, such as about once every 2 weeks. In some embodiments, administration of the anti-CSF1R antibody and the PD-1/PD-L1 inhibitor results in a synergistic effect on tumor growth, weight, and/or volume compared in a mouse xenograft model for pancreatic cancer (such as a model comprising KRas^{G12D}/Ink4a^{-/-} murine

pancreatic ductal adenocarcinoma (PDAC) cells) compared to administration of the anti-CSF1R antibody or PD-1/PD-L1 inhibitor alone.

[019] In some embodiments of the uses and methods, malignant glioma (e.g. glioblastoma or gliosarcoma) is treated with the anti-CSF1R antibody (for instance, an anti-CSF1R antibody as described herein, such as an antibody comprising the heavy and light chain CDRs of HuAB1) and the PD-1/PD-L1 inhibitor (for instance, an anti-PD-1 antibody comprising the heavy chain and light chain CDRs of nivolumab or pembrolizumab or a PD-1/PD-L1 inhibitor fusion protein or peptide such as AMP-224 or AUR-012). In some embodiments, the patient has previously been treated with surgery, radiotherapy, and/or temozolomide. In some embodiments, the patient has Grade IV malignant glioma. In some embodiments, the patient has not had prior exposure to a PD-1/PD-L1 inhibitor, and in other embodiments, the patient is refractory to PD-1/PD-L1 inhibitor treatment. In some embodiments, the anti-CSF1R antibody is administered at a dose of about 0.1, about 0.3, about 0.5, about 1, about 2, about 3, about 4, about 5 or about 10 mg/kg. In some embodiments, the PD-1/PD-L1 inhibitor is administered at a dose of 0.1-10 mg/kg, such as, for example about 0.1, about 0.3, about 0.5, about 1, about 2, about 3, about 4, about 5 or about 10 mg/kg mg/kg. In some embodiments, the anti-CSF1R antibody and the PD-1/PD-L1 inhibitor are administered, for example at one of the above doses, once per 1, 2, 3, 4, or 5 weeks, such as about once every 2 weeks. In some embodiments, administration of the anti-CSF1R antibody and the PD-1/PD-L1 inhibitor results in a synergistic effect on tumor growth, weight, and/or volume compared in a mouse xenograft model for glioma compared to administration of the anti-CSF1R antibody or PD-1/PD-L1 inhibitor alone.

[020] In some embodiments, the use and method further comprises administering one or more additional anti-cancer agents. In certain embodiments, the anti-cancer agent is selected from the group consisting of an antibody or antigen-binding portion thereof that binds specifically to CTLA-4 ("anti-CTLA-4 antibody or antigen-binding portion thereof") and inhibits CTLA-4 activity, a chemotherapy, a platinum-based doublet chemotherapy, a tyrosine kinase inhibitor, an anti-VEGF inhibitor, an Indoleamine-pyrrole 2,3-dioxygenase (IDO) inhibitor, or any combination thereof. In one embodiment, the anti-cancer agent is ipilimumab.

[021] In some embodiments, compositions are provided, comprising an anti-CSF1R antibody and a PD-1/PD-L1 inhibitor. In some embodiments, the PD-1/PD-L1 inhibitor is an antibody. In some embodiments, the PD-1/PD-L1 inhibitor is an anti-PD-1 antibody.

[021a] In one aspect, there is provided a composition comprising an anti-CSF1R antibody and an anti-PD-1 antibody wherein:

the anti-CSF1R antibody is selected from:

a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 39 and a light chain comprising the sequence of SEQ ID NO: 46;

b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16, and an HC CDR3 having the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; and

c) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 53 and a light chain comprising the sequence of SEQ ID NO: 60, and

the anti-PD-1 antibody is selected from:

a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 100 and a light chain comprising the sequence of SEQ ID NO: 102;

b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 105, an HC CDR2 having the sequence of SEQ ID NO: 107, and an HC CDR3 having the sequence of SEQ ID NO: 109, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 112, a LC CDR2 having the sequence of SEQ ID NO: 114, and a LC CDR3 having the sequence of SEQ ID NO: 116; and

c) an antibody comprising a heavy chain comprising the sequences of SEQ ID NOs: 100 and 101 and a light chain comprising the sequences of SEQ ID NOs: 102 and 103

[021b] In some embodiments, the anti-PD-1 antibody comprises the heavy chain and light chain CDRs

of an antibody selected from nivolumab and pembrolizumab. In some embodiments, the anti-PD-1 antibody comprises the heavy chain and light chain variable regions of an antibody selected from nivolumab and pembrolizumab. In some embodiments, the anti-PD-1 antibody is selected from nivolumab and pembrolizumab. In some embodiments, the PD-1/PD-L1 inhibitor is an anti-PD-L1 antibody. In some embodiments, the anti-PD-L1 antibody comprises the heavy chain and light chain CDRs of an antibody selected from BMS-936559, MPDL3280A, MEDI4736, and MSB0010718C. In some embodiments, the anti-PD-1 antibody comprises the heavy chain and light chain variable regions of an antibody selected from BMS-936559, MPDL3280A, MEDI4736, and MSB0010718C. In some embodiments, the anti-PD-1 antibody is selected from BMS-936559, MPDL3280A, MEDI4736, and MSB0010718C. In some embodiments, the PD-1/PD-L1 inhibitor is a fusion protein. In some embodiments, the fusion protein is AMP-224.

[022] In any of the compositions, uses or methods described herein, the antibody heavy chain and/or the antibody light chain of the anti-CSF1R antibody may have the structure described below.

[023] In any of the compositions, uses or methods described herein, the anti-CSF1R antibody heavy chain may comprise a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from SEQ ID NOs: 9, 11, 13, and 39 to 45. In any of the uses or methods described herein, the anti-CSF1R antibody light chain may comprise a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from SEQ ID NOs: 10, 12, 14, and 46 to 52. In any of the compositions, uses or methods described herein, the anti-CSF1R antibody heavy chain may comprise a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from SEQ ID NOs: 9, 11, 13, and 39 to 45, and the anti-CSF1R antibody light chain may comprise a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from SEQ ID NOs: 10, 12, 14, and 46 to 52.

[024] In any of the compositions, uses or methods described herein, the anti-CSF1R antibody HC CDR1, HC CDR2, and HC CDR3 may comprise a set of sequences selected from: (a) SEQ ID NOs: 15, 16, and 17; (b) SEQ ID NOs: 21, 22, and 23; and (c) SEQ ID NOs: 27, 28, and 29. In any of the compositions, uses or methods described herein, the anti-CSF1R antibody LC CDR1, LC CDR2, and LC CDR3 may comprise a set of sequences selected from: (a) SEQ ID NOs: 18, 19, and 20; (b) SEQ ID NOs: 24, 25, and 26; and (c) SEQ ID NOs: 30, 31, and 32.

[025] In any of the compositions, uses or methods described herein, the anti-CSF1R antibody heavy chain may comprise an HC CDR1, HC CDR2, and HC CDR3, wherein the HC CDR1, HC CDR2, and HC CDR3 comprise a set of sequences selected from: (a) SEQ ID NOs: 15, 16, and 17; (b) SEQ ID NOs: 21, 22, and 23; and (c) SEQ ID NOs: 27, 28, and 29; and the light chain may comprise an LC CDR1, LC CDR2, and LC CDR3, wherein the LC CDR1, LC CDR2, and LC CDR3 comprise a set of sequences selected from: (a) SEQ ID NOs: 18, 19, and 20; (b) SEQ ID NOs: 24, 25, and 26; and (c) SEQ ID NOs: 30, 31, and 32.

[026] In any of the compositions, uses or methods described herein, the anti-CSF1R antibody may comprise: (a) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 9 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 10; (b) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 11 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 12; (c) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 13 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 14; (d) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 39 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 46; (e) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 40 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 46; (f) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 41 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 46; (g) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 39 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 47; (h) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 40 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 47; (i) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 41 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 47; and (j) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least

99%, or 100% identical to SEQ ID NO: 42 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 48; (k) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 42 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 49; (l) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 42 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 50; (m) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 43 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 48; (n) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 43 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 49; (o) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 43 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 50; (p) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 44 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 51; (q) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 44 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 52; (r) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 45 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 51; or (s) a heavy chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 45 and a light chain comprising a sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 52.

[027] In any of the compositions, uses or methods described herein, the anti-CSF1R antibody may comprise: (a) a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16, and an HC CDR3 having the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; (b) a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 21, an HC CDR2

having the sequence of SEQ ID NO: 22, and an HC CDR3 having the sequence of SEQ ID NO: 23, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 24, a LC CDR2 having the sequence of SEQ ID NO: 25, and a LC CDR3 having the sequence of SEQ ID NO: 26; or (c) a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 27, an HC CDR2 having the sequence of SEQ ID NO: 28, and an HC CDR3 having the sequence of SEQ ID NO: 29, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 30, a LC CDR2 having the sequence of SEQ ID NO: 31, and a LC CDR3 having the sequence of SEQ ID NO: 32.

[028] In any of the compositions, uses or methods described herein, the anti-CSF1R antibody may comprise: (a) a heavy chain comprising a sequence of SEQ ID NO: 53 and a light chain comprising a sequence of SEQ ID NO: 60; (b) a heavy chain comprising a sequence of SEQ ID NO: 53 and a light chain comprising a sequence of SEQ ID NO: 61; or (c) a heavy chain comprising a sequence of SEQ ID NO: 58 and a light chain comprising a sequence of SEQ ID NO: 65. In some embodiments, an antibody comprises a heavy chain and a light chain, wherein the antibody comprises: (a) a heavy chain consisting of the sequence of SEQ ID NO: 53 and a light chain consisting of the sequence of SEQ ID NO: 60; (b) a heavy chain consisting of the sequence of SEQ ID NO: 53 and a light chain consisting of the sequence of SEQ ID NO: 61; or (c) a heavy chain consisting of the sequence of SEQ ID NO: 58 and a light chain consisting of the sequence of SEQ ID NO: 65.

[029] In any of the compositions, uses or methods described herein, the anti-CSF1R antibody may bind to human CSF1R and/or binds to cynomolgus CSF1R. In any of the compositions, uses or methods described herein, the anti-CSF1R antibody may block ligand binding to CSF1R. In any of the compositions, uses or methods described herein, the anti-CSF1R antibody may block binding of CSF1 and/or IL-34 to CSF1R. In any of the compositions, uses or methods described herein, the anti-CSF1R antibody may block binding of both CSF1 and IL-34 to CSF1R. In any of the compositions, uses or methods described herein, the anti-CSF1R antibody may inhibit ligand-induced CSF1R phosphorylation. In any of the compositions, uses or methods described herein, the anti-CSF1R antibody may inhibit CSF1- and/or IL-34-induced CSF1R phosphorylation. In any of the compositions, uses or methods described herein, the anti-CSF1R antibody may bind to human CSF1R with an affinity (K_D) of less than 1 nM. In any of the compositions, uses or methods described herein, the anti-CSF1R antibody may inhibit monocyte proliferation and/or survival responses in the presence of CSF1 or IL-34.

[030] In any of the compositions, uses or methods described herein, the PD-1/PD-L1 inhibitor may be an antibody, such as an anti-PD-1 antibody, with a structure described below.

[031] In any of the compositions, uses or methods described herein, the PD-1/PD-L1 inhibitor may be an antibody with an antibody heavy chain comprising a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from SEQ ID NOs: 100 and 101. In any of the uses or methods described herein, the PD-1/PD-L1 inhibitor may be an antibody with an antibody light chain comprising a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from SEQ ID NOs: 102 and 103.

[032] In any of the compositions, uses or methods described herein, the PD-1/PD-L1 inhibitor may be an antibody with heavy chain (HC) CDR1, HC CDR2, and HC CDR3 comprising a set of sequences selected from SEQ ID NOs: 105, 107, and 109. In any of the compositions, uses or methods described herein, the PD-1/PD-L1 inhibitor may be an antibody with light chain (LC) CDR1, LC CDR2, and LC CDR3 comprising a set of sequences selected from SEQ ID NOs: 112, 114, and 116.

[033] In any of the compositions, uses or methods described herein, the PD-1/PD-L1 inhibitor may be an antibody comprising: (a) a heavy chain comprising a variable region sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 100 and a light chain comprising a variable region sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 102; (b) a heavy chain comprising a constant region sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 101 and a light chain comprising a constant region sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 103; (c) a heavy chain comprising a variable region sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 100 and a light chain comprising a variable region sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 102; and/or (d) a heavy chain comprising a constant region sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 101 and a light chain comprising a constant region sequence that is at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 103.

[034] In any of the compositions, uses or methods described herein, the PD-1/PD-L1 inhibitor may be an antibody comprising: a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 105, an HC CDR2 having the sequence of SEQ ID NO: 107, and an HC CDR3 having the sequence of SEQ ID NO: 109, and a light chain

comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 112, a LC CDR2 having the sequence of SEQ ID NO: 114, and a LC CDR3 having the sequence of SEQ ID NO: 116. In any of the compositions, uses or methods described herein, the PD-1/PD-L1 inhibitor may be an antibody comprising: a heavy chain comprising a heavy chain (HC) FR1 having the sequence of SEQ ID NO: 104, an HC FR2 having the sequence of SEQ ID NO: 106, an HC FR3 having the sequence of SEQ ID NO: 108, and an HC FR4 having the sequence of SEQ ID NO: 110; and/or, a light chain comprising a light chain (LC) FR1 having the sequence of SEQ ID NO: 111, a LC FR2 having the sequence of SEQ ID NO: 113, a LC FR3 having the sequence of SEQ ID NO: 115, and a LC FR4 having the sequence of SEQ ID NO: 117.

[035] In any of the compositions, uses or methods described herein, the anti-CSF1R antibody or PD-1/PD-L1 inhibitor may be a humanized or chimeric antibody. In any of the compositions, uses or methods described herein, the anti-CSF1R or PD-1/PD-L1 inhibitor may be selected from a Fab, an Fv, an scFv, a Fab', and a (Fab')₂. In any of the compositions, uses or methods described herein, the anti-CSF1R or PD-1/PD-L1 inhibitor may be selected from an IgA, an IgG, and an IgD. In any of the compositions, uses or methods described herein, the anti-CSF1R antibody or PD-1/PD-L1 inhibitor may be an IgG. In any of the uses or methods described herein, the antibody may be an IgG1, IgG2 or IgG4.

[036] In any of the uses or methods described herein, the tumor may or may not express PD-L1. In some embodiments, the tumor is PD-L1 positive. In other embodiments, the tumor is PD-L1 negative. In any of the uses or methods described herein, the tumor may or may not express PD-L2. In some embodiments, the tumor is PD-L2 positive. In other embodiments, the tumor is PD-L2 negative.

BRIEF DESCRIPTION OF THE FIGURES

[037] **FIG. 1A-C** show an alignment of the humanized heavy chain variable regions for each of humanized antibodies huAb1 to huAb16, as discussed in Example 1. Boxed residues are amino acids in the human acceptor sequence that were changed back to the corresponding mouse residue.

[038] **FIG. 2A-C** show an alignment of the humanized light chain variable regions for each of humanized antibodies huAb1 to huAb16, as discussed in Example 1. Boxed amino acids are residues in the human acceptor sequence that were changed back to the corresponding mouse residue.

[039] **FIG. 3** is a heat map showing the correlation between CSF1R expression and Tregs, PD-L1/PD-1 expression, and CD8+ T cells in various cancers.

CLAIMS

1. 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 anti-CSF1R antibody and anti-PD-1 antibody are to be administered concurrently or sequentially to the subject; and wherein:
the anti-CSF1R antibody is selected from:
 - a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 39 and a light chain comprising the sequence of SEQ ID NO: 46;
 - b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16, and an HC CDR3 having the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; and
 - c) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 53 and a light chain comprising the sequence of SEQ ID NO: 60, and
the anti-PD-1 antibody is selected from:
 - a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 100 and a light chain comprising the sequence of SEQ ID NO: 102;
 - b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 105, an HC CDR2 having the sequence of SEQ ID NO: 107, and an HC CDR3 having the sequence of SEQ ID NO: 109, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 112, a LC CDR2 having the sequence of SEQ ID NO: 114, and a LC CDR3 having the sequence of SEQ ID NO: 116; and
 - c) an antibody comprising a heavy chain comprising the sequences of SEQ ID NOs: 100 and 101 and a light chain comprising the sequences of SEQ ID NOs: 102 and 103.
2. The use according to claim 1, wherein the anti-PD-1 antibody is nivolumab.
3. The use according to claim 1 or 2, wherein the anti-CSF1R antibody and the anti-PD-1 antibody are to be administered concurrently.
4. The use according to claim 1 or 2, wherein one or more doses of the anti-PD-1 antibody are to be administered prior to administering the anti-CSF1R antibody.
5. The use according to claim 4, wherein the subject received a complete course of anti-PD-1 antibody therapy prior to administration of the anti-CSF1R antibody and the anti-CSF1R antibody is optionally to be administered during a second course of anti-PD-1 antibody therapy.

6. The use according to any one of claims 3 to 5, wherein at least one dose of the anti-PD-1 antibody is to be administered concurrently with the anti-CSF1R inhibitor.

7. The use according to claim 1 or 2, wherein one or more doses of the anti-CSF1R antibody are to be administered prior to administering the anti-PD-1 antibody.

8. The use according to claim 7, wherein the subject received at least two, at least three, or at least four doses of the anti-CSF1R antibody prior to administration of the anti-PD-1 antibody and optionally at least one dose of the anti-CSF1R antibody is to be administered concurrently with the anti-PD-1 antibody.

9. The use according to any one of the preceding claims, wherein the anti-CSF1R antibody is to be administered at a dose of about 0.1, about 0.3, about 0.5, about 1, about 2, about 3, about 4, about 5, or about 10 mg/kg.

10. The use according to any one of the preceding claims, wherein the anti-PD-1 antibody is to be administered at a dose of about 0.5-10 mg/kg, such as at a dose of about 0.5, about 1, about 2, about 3, about 4, about 5, or about 10 mg/Kg.

11. The use according to any one of the preceding claims, wherein the anti-CSF1R antibody and the anti-PD-1 antibody are to be administered once per 1, 2, 3, 4, or 5 weeks, such as once per week, or such as once every 2 weeks, or once every 3 weeks.

12. The use according to any one of the preceding claims, wherein the cancer is selected from non-small cell lung cancer, melanoma, squamous cell carcinoma of the head and neck, ovarian cancer, pancreatic cancer, renal cell carcinoma, hepatocellular carcinoma, bladder cancer, malignant glioma, colorectal cancer, and endometrial cancer.

13. The use according to any one of the preceding claims, wherein the cancer is recurrent or progressive after a therapy selected from surgery, chemotherapy, radiation therapy, or a combination thereof.

14. The use according to any one of the preceding claims, wherein administration of the anti-CSF1R antibody and the anti-PD-1 antibody in a mouse xenograft model of the cancer results in synergistic inhibition of tumor growth.

15. The use according to claim 14, wherein the cancer is a colon, rectum, or colorectal cancer and the mouse xenograft model comprises colorectal carcinoma cells, such as MC38 colorectal carcinoma cells; or

wherein the cancer is a pancreatic cancer and the mouse xenograft model comprises murine pancreatic ductal adenocarcinoma (PDAC) cells, such as KRas^{G12D}/Ink4a^{-/-} pancreatic ductal adenocarcinoma cells.

16. The use according to any of the preceding claims, wherein the patient has non-

small cell lung cancer, melanoma, squamous cell carcinoma of the head and neck, ovarian cancer, pancreatic cancer, renal cell carcinoma, hepatocellular carcinoma, bladder cancer, malignant glioma, colorectal cancer, or endometrial cancer; and wherein the anti-CSF1R antibody is to be administered at a dose of about 1, about 2, or about 3 mg/kg every two weeks and the anti-PD-1 antibody is to be administered at a dose of about 3 mg/kg every two weeks.

17. The use according to claim 16, wherein the patient has non-small cell lung cancer, melanoma, squamous cell carcinoma of the head and neck, ovarian cancer, pancreatic cancer, renal cell carcinoma, hepatocellular carcinoma, bladder cancer, malignant glioma, colorectal cancer, or endometrial cancer; and wherein the anti-CSF1R antibody and the anti-PD-1 antibody are each to be administered at a dose of about 3 mg/kg every two weeks.

18. The use according to claim 16 or 17, wherein the patient has pancreatic cancer and wherein the anti-CSF1R antibody and the anti-PD-1 antibody are each to be administered at a dose of about 3 mg/kg every two weeks.

19. The use according to claim 16, 17, or 18, wherein the anti-CSF1R antibody comprises a heavy chain comprising the sequence of SEQ ID NO: 53 and a light chain comprising the sequence of SEQ ID NO: 60 and the anti-PD-1 antibody is nivolumab.

20. A composition comprising an anti-CSF1R antibody and an anti-PD-1 antibody wherein:

the anti-CSF1R antibody is selected from:

a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 39 and a light chain comprising the sequence of SEQ ID NO: 46;

b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 15, an HC CDR2 having the sequence of SEQ ID NO: 16, and an HC CDR3 having the sequence of SEQ ID NO: 17, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 18, a LC CDR2 having the sequence of SEQ ID NO: 19, and a LC CDR3 having the sequence of SEQ ID NO: 20; and

c) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 53 and a light chain comprising the sequence of SEQ ID NO: 60, and

the anti-PD-1 antibody is selected from:

a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO: 100 and a light chain comprising the sequence of SEQ ID NO: 102;

b) an antibody comprising a heavy chain comprising a heavy chain (HC) CDR1 having the sequence of SEQ ID NO: 105, an HC CDR2 having the sequence of SEQ ID NO:

107, and an HC CDR3 having the sequence of SEQ ID NO: 109, and a light chain comprising a light chain (LC) CDR1 having the sequence of SEQ ID NO: 112, a LC CDR2 having the sequence of SEQ ID NO: 114, and a LC CDR3 having the sequence of SEQ ID NO: 116; and

c) an antibody comprising a heavy chain comprising the sequences of SEQ ID NOs: 100 and 101 and a light chain comprising the sequences of SEQ ID NOs: 102 and 103.