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(54) Title: DOSAGE REGIMES FOR ANTI-M-CSF ANTIBODIES AND USES THEREOF

(57) Abstract: The invention generally relates to dosage regimes of anti-macrophage colony stimulating factor 1 (M-CSF) antibodies, such as lacnotuzumab, used in methods of treatment of cancer in a subject, as well as dosage regimes of anti-M-CSF antibodies, such as lacnotuzumab, for use in treating cancer. The invention further generally relates to dosage regimes of combinations of agents, such as combinations comprising anti-M-CSF antibodies, such as lacnotuzumab, and at least one or more of gemcitabine, nab-paclitaxel and a PD-1 inhibitor (such as spartalizumab).

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DOSAGE REGIMES FOR ANTI-M-CSF ANTIBODIES AND USES THEREOF

INTRODUCTION

The invention generally relates to dosage regimes of anti-macrophage colony stimulating factor 1 (M-CSF) antibodies, used in methods of treatment of cancer in a subject, as well as dosage regimes of anti-M-CSF antibodies for use in treating cancer. The invention further generally relates to dosage regimes of combinations of agents, such as combinations comprising anti-M-CSF antibodies and at least one or more of gemcitabine, nab-paclitaxel and a PD-1 inhibitor.

BACKGROUND OF THE INVENTION

Effective treatments for cancer solid tumours are needed, such as treatments for pancreatic cancer, endometrial cancer, melanoma and triple negative breast cancer (TNBC). Approximately 95% of pancreatic cancers are adenocarcinoma (exocrine pancreatic cancer), with the remaining 5% being a heterogeneous mix of five major sub-types (e.g., neuroendocrine). Pancreatic ductal adenocarcinoma (PDAC) represents a significant public health burden, being the fourth-leading cause of cancer-related death, with an estimated 43,090 deaths and 53,670 new cases in 2017 in the US (Siegel et al. 2017). Worldwide, PDAC is the twelfth most frequent cancer with about 338,000 new cases reported in 2012. However, it was the seventh most common cause of cancer-related deaths due to its very poor prognosis (Ferlay et al. 2015). Approximately 75% of patients with PDAC present with locally advanced or metastatic disease at diagnosis, with the main metastatic sites being the liver, the lungs and the peritoneum. Systemic therapy options and optimal supportive care are provided to these patients with the aim to induce disease regression, extend life and alleviate symptoms. However, for all stages combined, the overall 5-year survival rate is 8%, decreasing to 3% in patients presenting with advanced disease (ACS Facts and Figures, 2017). This extremely poor prognosis highlights the urgent need for the development of chemotherapy treatment regimes, with acceptable safety and tolerability profiles, to treat pancreatic cancer.

SUMMARY OF THE INVENTION

The present invention provides an isolated antibody or antigen binding fragment capable of binding to macrophage colony stimulating factor 1 (M-CSF) for use at a dose of about 5 mg/kg once every two weeks, or at a dose of about 7.5 mg /kg once every three weeks or at a dose of about 7.5 mg /kg once every four weeks or at a dose of about 10 mg /kg once every four weeks in treating a cancer in a subject, wherein the antibody or antigen

binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

Also the present invention provides a method of treating a cancer in a subject, the method comprising administering to the subject an isolated antibody or antigen binding fragment capable of binding to macrophage colony stimulating factor 1 (M-CSF) at a dose of about 5 mg/kg once every two weeks, or at a dose of about 7.5 mg /kg once every three weeks or at a dose of about 7.5 mg /kg once every four weeks or at a dose of about 10 mg /kg once every four weeks, wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

In one embodiment the present invention provides an isolated antibody or antigen binding fragment capable of binding to macrophage colony stimulating factor 1 (M-CSF) for use at dose of about 5 mg /kg once every two weeks in treating a cancer in a subject, wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11. In another embodiment the present invention provides an isolated antibody or antigen binding fragment capable of binding to macrophage colony stimulating factor 1 (M-CSF) for use at dose of about 7.5 mg /kg once every three weeks in treating a cancer in a subject, wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11. In a specific embodiment the present invention provides an isolated antibody or antigen binding fragment capable of binding to macrophage colony stimulating factor 1 (M-CSF) for use at dose of about 7.5 mg /kg once every four weeks in treating a cancer in a

subject, wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11. In another embodiment the present invention provides an isolated antibody or antigen binding fragment capable of binding to macrophage colony stimulating factor 1 (M-CSF) for use at a dose of about 10 mg /kg once every four weeks in treating a cancer in a subject, wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

Also in an embodiment the present invention provides a method of treating a cancer in a subject, the method comprising administering to the subject an isolated antibody or antigen binding fragment capable of binding to macrophage colony stimulating factor 1 (M-CSF) at dose of about 5 mg /kg once every two weeks wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11. In another embodiment the present invention provides a method of treating a cancer in a subject, the method comprising administering to the subject an isolated antibody or antigen binding fragment capable of binding to macrophage colony stimulating factor 1 (M-CSF) at dose of about 7.5 mg /kg once every three weeks wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11. Also in a specific embodiment the present invention provides a method of treating a cancer in a subject, the method comprising administering to the subject an isolated antibody or antigen binding fragment capable of binding to macrophage colony stimulating factor 1 (M-CSF) at dose of about 7.5 mg /kg once every four weeks wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and

a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11. In another embodiment the present invention provides a method of treating a cancer in a subject, the method comprising administering to the subject an isolated antibody or antigen binding fragment capable of binding to macrophage colony stimulating factor 1 (M-CSF) at a dose of about 10 mg /kg once every four weeks, wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

In a preferred embodiment antibody or antigen binding fragment capable of binding to M-CSF comprises a VH comprising the amino acid sequence of SEQ ID NO: 15 and a VL comprising the amino acid sequence of SEQ ID NO: 14. In another preferred embodiment the antibody or antigen binding fragment capable of binding to M-CSF comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 4 and a light chain comprising the amino acid sequence of SEQ ID NO: 5. In a particular embodiment, the antibody or antigen binding fragment capable of binding to M-CSF is lacnotuzumab (MCS110).

In an embodiment of the invention, the cancer is a solid tumour. In a specific embodiment of the invention, the cancer is selected from the group consisting of pancreatic cancer, melanoma, breast cancer and endometrial cancer. In another specific embodiment, the breast cancer is triple negative breast cancer (TNBC). In a specific embodiment the TNBC may be advanced or metastatic TNBC. In yet another specific embodiment, the melanoma has been previously resistant to PD-1/PD-L1 directed therapy. In a further specific embodiment, the cancer is endometrial cancer. In one preferred embodiment, the cancer is pancreatic cancer. In another preferred embodiment, the pancreatic cancer is pancreatic adenocarcinoma. In yet another preferred embodiment the pancreatic cancer is metastatic pancreatic ductal adenocarcinoma. In a specific embodiment, the antibody or antigen binding fragment for use or method of treating cancer is for use in a method of first line (1L) therapy to treat metastatic pancreatic ductal adenocarcinoma.

In an embodiment of the invention, the antibody or antigen binding fragment capable of binding to M-CSF is used in combination with a PD-1 inhibitor. Preferably, the PD-1 inhibitor is selected from the group consisting of spartalizumab (also known as PDR001), nivolumab, pembrolizumab, pidilizumab, MEDI0680, REGN2810, PF-06801591, BGB-A317, BGB-108, INCHR1210, TSR-042, and AMP-224. In a particular embodiment, the PD-1 inhibitor is spartalizumab (PDR001). In one embodiment of the invention, the PD-1 inhibitor is used at a dose of about 300 mg once every three weeks. In an alternative embodiment of the invention, the PD-1 inhibitor is used of about 400 mg once every four weeks.

In another embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is used at a dose of about 7.5 mg/kg once every three weeks and the PD-1 inhibitor is used at a dose of about 300 mg once every three weeks. In yet another embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is used at a dose of about 7.5 mg /kg once every four weeks and the PD-1 inhibitor is used at a dose of about 400 mg once every four weeks. In a further embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is used at a dose of about 10 mg /kg once every four weeks and the PD-1 inhibitor is used at a dose of about 400 mg once every four weeks.

In another embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is used at a dose of about 5 mg/kg once every two weeks and the PD-1 inhibitor is used at a dose of about 300 mg once every three weeks or the antibody or antigen binding fragment capable of binding to M-CSF is used at a dose of about 5 mg /kg once every two weeks and the PD-1 inhibitor is used at a dose of about 400 mg once every four weeks.

In a specific embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is lacnotuzumab and is used at a dose of about 7.5 mg/kg once every three weeks and the PD-1 inhibitor is used at a dose of about 300 mg once every three weeks. In yet another embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is lacnotuzumab and is used at a dose of about 7.5 mg /kg once every four weeks and the PD-1 inhibitor is used at a dose of about 400 mg once every four weeks. In a further embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is lacnotuzumab and is used at a dose of about 10 mg /kg once every four weeks and the PD-1 inhibitor is used at a dose of about 400 mg once every four weeks.

In a specific embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is lacnotuzumab and is used at a dose of about 5 mg/kg once every two weeks and the PD-1 inhibitor is used at a dose of about 300 mg once every three weeks. In yet another embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is lacnotuzumab and is used at a dose of about 5 mg /kg once every two weeks and the PD-1 inhibitor is used at a dose of about 400 mg once every four weeks.

In a particular embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is lacnotuzumab and is used at a dose of about 7.5 mg/kg once every three weeks and the PD-1 inhibitor is spartalizumab and is used at a dose of about 300 mg once every three weeks. In yet another embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is lacnotuzumab and is used at a dose of about 7.5 mg /kg once every four weeks and the PD-1 inhibitor is spartalizumab and is used at a dose of about 400 mg once every four weeks. In a further embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is lacnotuzumab and is used at a dose of about 10 mg /kg once every four weeks and the PD-1 inhibitor is spartalizumab and is used at a dose of about 400 mg once every four weeks.

In one embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is used in combination with gemcitabine. In a specifc embodiment the gemcitabine is administered as 1000 mg/m^2 three times within four weeks.

In another embodiment of the invention, the antibody or antigen binding fragment capable of binding to M-CSF is used in combination with paclitaxel. In a specific embodiment of the invention, the antibody or antigen binding fragment capable of binding to M-CSF is used in combination with nab-paclitaxel. In another specific embodiment, the nab-paclitaxel is administered as 125 mg/m^2 three times within four weeks.

In an embodiment of the invention the M-CSF antibody MCS110 (an antibody having the heavy chain variable region including the amino acids set forth in SEQ ID NO: 15 and the light chain variable region including the amino acids set forth in SEQ ID NO: 14) is administered to patients with pancreatic cancer in combination with gemcitabine, paclitaxel and optionally PDR001 (an antibody having the heavy chain variable region including the amino acids set forth in SEQ ID NO: 43 and the light chain variable region including the amino acids set forth in SEQ ID NO: 53).

In a further specific embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is lacnotuzumab and is used at a dose of about 10 mg/kg once every four weeks, and is used in combination with

a) gemcitabine that is administered as 1000 mg/m^2 three times within four weeks and
b) nab-paclitaxel that is administered as 125 mg/m^2 three times within four weeks.

In yet a further specific embodiment of the invention the antibody or antigen binding fragment capable of binding to M-CSF is lacnotuzumab and is used at a dose of about 10 mg/kg once every four weeks, and is used in combination with

a) gemcitabine that is administered as 1000 mg/m^2 three times within four weeks and
b) nab-paclitaxel that is administered as 125 mg/m^2 three times within four weeks and
c) PD-1 inhibitor that is spartalizumab and which is used at a dose of about 400 mg once every four weeks.

In another aspect the invention relates to a pharmaceutical composition or dose formulation comprising an antibody or antigen binding fragment capable of binding to M-CSF for use at a dose of about 7.5 mg /kg once every three weeks or at a dose of about 7.5 mg /kg once every four weeks or at a dose of about 10 mg /kg once every four weeks, in treating a cancer in a subject, wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

In another aspect the invention relates to a pharmaceutical composition or dose formulation comprising an antibody or antigen binding fragment capable of binding to M-CSF for use at a dose of about 5 mg /kg once every two weeks, in treating a cancer in a subject, wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

DEFINITIONS

As used in the specification and claims, the singular form “a”, “an” and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a cell” includes a plurality of cells, including mixtures thereof.

The term "antibody" as used herein refers to a molecule that specifically binds to or interacts with a given antigen (e.g. M-CSF) and has the format of a whole antibody. A whole antibody is a glycoprotein molecule comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Antibodies can be polyclonal or monoclonal, and may be derived from natural sources or from recombinant sources. The antibodies can be of any isotype (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass. The antibody may be monospecific or bispecific.

The terms “antigen binding fragment”, “antigen binding fragment thereof,” and the like, as used herein, refers to any antigen binding molecule that has a format related to a portion or portions of a whole antibody and has the ability to specifically bind to or interact with a given antigen (e.g. M-CSF). The binding or interaction is via at least one complementarity determining region (CDR). Examples of antigen binding fragments include, but are not limited to, molecules with the following formats: a Fab fragment, Fab’ fragment, a F(ab)2 fragment, a scFv fragment, a Fd fragment, a Fv fragment, Fab-scFv, a single domain antibody (dAb), diabody, single chain diabody (scDb), disulfide stabilized Diabody DsDB, tandem scFv, Dual Affinity Re-Targeting format antibody (DART), diabody-Fc fusion, scDb-Fc fusion, tandem scDb (TandAb), scDb-CH3 fusion, triabody, tetrabody, minibody, maxibody, nanobody, small modular immunopharmaceutical (SMIPs) and shark variable IgNAR domain. Molecules with combinations of any of these formats, as well as with mono or multi target specificity, such as bispecific and trispecific antibody formats are also encompassed within the expression "antigen binding fragment," as used herein. Antigen binding fragments can also be grafted into scaffolds based on polypeptides such as a fibronectin type III

(Fn3)(see U.S. Patent No.: 6,703,199, which describes fibronectin polypeptide minibodies).

The term "antigen-binding site" refers to the part of an antibody molecule that comprises determinants that form an interface that binds to the target (e.g. M-CSF) polypeptide, or an epitope thereof. With respect to proteins (or protein mimetics), the antigen-binding site typically includes one or more loops (of at least four amino acids or amino acid mimics) that form an interface that binds to the target (e.g. M-CSF) polypeptide. Typically, the antigen-binding site of an antibody molecule includes at least one or two CDRs and/or hypervariable loops, or more typically at least three, four, five or six CDRs and/or hypervariable loops.

The terms “complementarity determining region,” and “CDR,” as used herein refer to the sequences of amino acids within antibody variable regions that confer antigen specificity and binding affinity. In a preferred embodiment, there are three CDRs in each heavy chain variable region (HCDR1, HCDR2, HCDR3) and three CDRs in each light chain variable region (LCDR1, LCDR2, LCDR3). The precise amino acid sequence boundaries of a given CDR can be determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), “Sequences of Proteins of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (“Kabat” numbering scheme), Al-Lazikani et al., (1997) JMB 273, 927-948 (“Chothia” numbering scheme) and ImMunoGenTics (IMGT) numbering (Lefranc, M.-P., The Immunologist, 7, 132-136 (1999); Lefranc, M.-P. et al., Dev. Comp. Immunol., 27, 55-77 (2003) (“IMGT” numbering scheme). For example, for classic formats, under Kabat, the CDR amino acid residues in the heavy chain variable domain (VH) are numbered 31-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3); and the CDR amino acid residues in the light chain variable domain (VL) are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3). Under Chothia the CDR amino acids in the VH are numbered 26-32 (HCDR1), 52-56 (HCDR2), and 95-102 (HCDR3); and the amino acid residues in VL are numbered 26-32 (LCDR1), 50-52 (LCDR2), and 91-96 (LCDR3). By combining the CDR definitions of both Kabat and Chothia, the CDRs consist of amino acid residues 26-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3) in human VH and amino acid residues 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3) in human VL. Under IMGT the CDR amino acid residues in the VH are numbered approximately 26-35 (CDR1), 51-57 (CDR2) and 93-102 (CDR3), and the CDR amino acid residues in the VL are numbered approximately 27-32 (CDR1), 50-52 (CDR2), and 89-97 (CDR3) (numbering according to “Kabat”). Under IMGT, the CDR regions of an antibody can be determined using the program IMGT/DomainGap Align.

The term "human antibody" (or antigen binding fragment), as used herein, is intended to include antibodies (or antigen binding fragments) having variable regions in which both the framework and CDR regions are derived from sequences of human origin. Furthermore, if the antibody or antigen binding fragment contains a constant region, the constant region also is derived from such human sequences, e.g., human germline sequences, or mutated versions of human germline sequences. The human antibodies and antigen binding fragments of the invention may include some amino acid residues not encoded by human sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo).

A "humanized" antibody (or antigen-binding fragment), as used herein, is an antibody (or antigen binding fragment) that retains the reactivity of a non-human antibody while being less immunogenic in humans. This can be achieved, for instance, by retaining the non-human CDR regions and replacing parts of the antibody with their human counterparts (i.e., the constant region as well as the framework portions of the variable region). See, e.g., Morrison et al., Proc. Natl. Acad. Sci. USA, 81:6851-6855, 1984; Morrison and Oi, Adv. Immunol., 44:65-92, 1988; Verhoeyen et al., Science, 239:1534-1536, 1988; Padlan, Molec. Immun., 28:489-498, 1991; and Padlan, Molec. Immun., 31:169-217, 1994. An example of human engineering technology includes, but is not limited to Xoma technology disclosed in U.S. Pat. No. 5,766,886.

The terms "monoclonal antibody" (or antigen binding fragment) or "monoclonal antibody (or antigen binding fragment) composition" as used herein refer to a preparation of an antibody molecule (or antigen binding fragment) of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

The term "isolated antibody" (or antigen binding fragment), as used herein, refers to an antibody (or antigen binding fragment), that has been separated from at least one component of its natural environment. For example, an antibody that has been separated or removed from at least one component of an organism, or from a tissue or cell in which the antibody naturally exists or is naturally produced, is an "isolated antibody". In a preferred embodiment, isolated antibodies are antibodies that have been subjected to at least one purification or isolation step.

As used herein, "identity" in “sequence identity” refers to the sequence matching

between two polypeptides, molecules or between two nucleic acids. When a position in both of the two compared sequences is occupied by the same base or amino acid monomer subunit (for instance, if a position in each of the two DNA molecules is occupied by adenine, or a position in each of two polypeptides is occupied by a lysine), then the respective molecules are identical at that position. The "percentage (sequence) identity" between two sequences is a function of the number of matching positions shared by the two sequences divided by the number of positions compared x 100. A comparison is made when two sequences are aligned to give maximum identity.

Two sequences are "substantially identical" if two sequences have a specified percentage of amino acid residues or nucleotides that are the same (i.e., 60% identity, optionally 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99%, preferably 90%, 95%, 96%, 97%, 98% or 99%, identity over a specified region, or, when not specified, over the entire sequence), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection.

For sequence comparison, one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer program, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

Methods of alignment of sequences for comparison are well known in the art. Optimal alignment of sequences for comparison can be conducted, e.g., by the algorithm of Smith and Waterman (1970) Adv. Appl. Math. 2:482c, by the algorithm of Needleman and Wunsch, J. Mol. Biol. 48:443, 1970, by the search for similarity method of Pearson and Lipman, Proc. Nat'l. Acad. Sci. USA 85:2444, 1988, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by manual alignment and visual inspection (see, e.g., Brent et al., Current Protocols in Molecular Biology, John Wiley & Sons, Inc. (ringbou ed., 2003)).

Two examples of algorithms that are suitable for determining percent sequence identity

and sequence similarity are the well-known Basic Local Alignment Search Tool: BLAST and BLAST 2.0 algorithms, described in Altschul et al., J. Mol. Biol. 215:403-410, 1990 and Altschul et al., Nuc. Acids Res. 25:3389-3402, 1997. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. For example BLAST version 2.3.0 or BLAST version 2.4.0 may be used. For example, also different programs may be used depending on the sequence: BLASTP performs a protein-protein sequence comparison and BLASTN performs a nucleotide-nucleotide sequence comparison. One commonly used scoring matrix for BLAST polypeptide searches is BLOSUM-62. Different scoring matrices are available and optionally these may be used for the following peptide query lengths: query length <35:PAM-30 (gap/extension costs (9,1)); query length 35-50:PAM-70 (gap/extension costs (10,1)); query length 50-85;:BLOSUM-80 (gap/extension costs (10,1) and query length >85 BLOSUM-62 (gap/extension costs (11,1). The percent identity between two amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller (Comput. Appl. Biosci., 4:11-17, 1988) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (J. Mol, Biol. 48:444-453, 1970) algorithm which has been incorporated into the GAP program in the GCG software package, using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

The term "subject" includes human and non-human animals. Non-human animals include vertebrates, e.g., mammals and non-mammals, such as non-human primates, sheep, cats, horses, cows, chickens, dogs, mice, rats, goats, rabbits, and pigs. Preferably, the subject is human. Except when noted, the terms "patient" or "subject" are used herein interchangeably.

As used herein, the term “treat”, “treating" or "treatment" of any disease or disorder refers to alleviating or ameliorating the disease or disorder (i.e., slowing or arresting the development of the disease or at least one of the clinical symptoms thereof); or alleviating or ameliorating at least one physical parameter or biomarker associated with the disease or disorder, including those which may not be discernible to the patient. As used herein, the term “prevent”, “preventing" or “prevention” of any disease or disorder refers to the prophylactic treatment of the disease or disorder; or delaying the onset or progression of the disease or disorder.

As used herein, a subject is "in need of" a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

The term "nucleic acid" or "polynucleotide" refers to deoxyribonucleic acids (DNA) or ribonucleic acids (RNA) and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions), alleles, orthologs, SNPs, and complementary sequences as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer et al., Nucleic Acid Res. 19:5081 (1991); Ohtsuka et al., J. Biol. Chem. 260:2605-2608 (1985); and Rossolini et al., Mol. Cell. Probes 8:91-98 (1994)).

The terms "peptide," "polypeptide," and "protein" are used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprise a protein's or peptide's sequence. Polypeptides include any peptide or protein comprising two or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. "Polypeptides" include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion proteins, among others. A polypeptide includes a natural peptide, a recombinant peptide, or a combination thereof.

The term "about" when referring to a measurable value such as an amount, and the like, is meant to encompass variations of ±20% or in some instances ±10%, or in some instances ±5%, or in some instances ±1%, or in some instances ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

The term "functional variant" refers to polypeptides that have a substantially identical amino acid sequence to the naturally-occurring sequence, or are encoded by a substantially identical nucleotide sequence, and are capable of having one or more activities of the naturally-occurring sequence.

By "a combination" or "in combination with," it is not intended to imply that the therapy or the therapeutic agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope described herein. The therapeutic agents in the combination can be administered concurrently with, prior to, or subsequent to, one or more other additional therapies or therapeutic agents. The therapeutic agents or therapeutic protocol can be administered in any order. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. It will further be appreciated that the additional therapeutic agent utilized in this combination may be administered together in a single composition or administered separately in different compositions. The combination partners may thus be entirely separate pharmaceutical dosage forms or pharmaceutical compositions that are also sold independently of each other and where just instructions for their combined use are provided in the package equipment, e.g. leaflet or the like, or in other information e.g. provided to physicians and medical staff (e.g. oral communications, communications in writing or the like), for simultaneous or sequential use for being jointly active.

The term "Programmed Death 1" or "PD-1" include isoforms, mammalian, *e.g.*, human PD-1, species homologs of human PD-1, and analogs comprising at least one common epitope with PD-1. The amino acid sequence of PD-1, *e.g.*, human PD-1, is known in the art, *e.g.*, Shinohara T *et al.* (1994) *Genomics* 23(3):704-6; Finger LR, *et al. Gene* (1997) 197(1-2):177-87.

The term "jointly therapeutically effective" means that the anti M-CSF antibody and for example the PD-1 inhibitor, e.g., the anti PD-1 antibody, may be given simultaneously (in one dosage form or multiple dosage forms) or separately (in a chronologically staggered manner, especially a sequence-specific manner) in such time intervals that they prefer, in the subject, especially human, to be treated, and still show an efficacious interaction. In one embodiment, the combination when administered shows an improved therapeutic response when compared to the therapeutic response when administered as a monotherapy to a subject with cancer.

The terms “co-administration” or “combined administration” or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (e.g. a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration and/or at the same time.

The term “non-fixed combination” means that the active ingredients are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two antibodies in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients. The term “non-fixed combination” thus defines especially a “kit of parts” in the sense that the combination partners as defined herein can be dosed independently of each other or by use of different fixed combinations with distinguished amounts of the combination partners, i.e. simultaneously or at different time points, where the combination partners may also be used as entirely separate pharmaceutical dosage forms or pharmaceutical formulations that are also sold independently of each other and just instructions of the possibility of their combined use is or are provided in the package equipment, e.g. leaflet or the like, or in other information e.g. provided to physicians and medical staff. The independent formulations or the parts of the kit of parts can then, e.g. be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Very preferably, the time intervals are chosen such that the effect on the treated disease in the combined use of the parts is larger than the effect that would be obtained by use of only any one of the combination partners (i) and (ii), thus being jointly active. The ratio of the total amounts of the combination partner (i) to the combination partner (ii) to be administered in the combined preparation can be varied, e.g. in order to cope with the needs of a patient sub-population to be treated or the needs of the single patient which different needs can be due to age, sex, body weight, etc. of the patients.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, isotonic and absorption delaying agents, and the like that are physiologically compatible. The carrier can be suitable for intravenous, intramuscular, subcutaneous, parenteral, rectal, spinal or epidermal administration (*e.g.* by injection or infusion).

The term "inhibition," "inhibitor," or "antagonist" includes a reduction in a certain parameter, *e.g.*, an activity, of a given molecule, *e.g.*, an immune checkpoint inhibitor. For example, inhibition of an activity, *e.g.*, a PD-1 or PD-L1 activity, of at least 5%, 10%, 20%, 30%, 40% or more is included by this term. Thus, inhibition need not be 100%.

The term "anti-cancer effect" refers to a biological effect which can be manifested by various means, including but not limited to, *e.g.,* a decrease in tumour volume, a decrease in the number of cancer cells, a decrease in the number of metastases, an increase in life expectancy, decrease in cancer cell proliferation, decrease in cancer cell survival, or amelioration of various physiological symptoms associated with the cancerous condition. An "anti-cancer effect" can also be manifested by the ability of the peptides, polynucleotides, cells and antibodies in prevention of the occurrence of cancer in the first place.

The term "anti-tumour effect" refers to a biological effect that can be manifested by various means, including but not limited to, *e.g.,* a decrease in tumour volume, a decrease in the number of tumour cells, a decrease in tumour cell proliferation, or a decrease in tumour cell survival.

The term "cancer" refers to a disease characterized by the rapid and uncontrolled growth of aberrant cells. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body. Preferably the cancer is selected from the group consisting of pancreatic cancer, melanoma, breast cancer and endometrial cancer. The terms "tumour" and "cancer" are used interchangeably herein, *e.g.,* both terms encompass solid and liquid, *e.g.,* diffuse or circulating, tumours. As used herein, the term "cancer" or "tumour" includes premalignant, as well as malignant cancers and tumours.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those

described herein can be used to practice the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is generally directed to dosage regimes of an anti-M-CSF antibody that can be used to treat cancers. In a specific embodiment the M-CSF antibody is dosed in combination with a PD-1 inhibitor, such as an anti-PD-1 antibody. In another specific embodiment the M-CSF antibody, is dosed together with the agents gemcitabine and/or paclitaxel, preferably nab-paclitaxel. While not wishing to be bound by theory the use of the dosage regime disclosed herein to treat a particular cancer is believed to be advantageous as it affects the immune response rescuing T cell anti-tumour response and expanding the endogenous anti-tumour response of T cells. Tumour associated macrophages (TAMs) in the tumour microenvironment are associated with poorer response to chemotherapy and a worse prognosis. The use of the anti-M-CSF antibody releases the break from the T cell compartment by depleting M2 macrophages which can suppress T cell function and proliferation through the production of immunomodulatory cytokines.

Antibodies to M-CSF

The various forms of M-CSF as described below function by binding to its receptor (M-CSFR) on target cells. M-CSFR is a membrane spanning molecule with five extracellular immunoglobulin-like domains, a transmembrane domain and an intracellular interrupted Src related tyrosine kinase domain. M-CSFR is encoded by the c-fms proto-oncogene. Binding of M-CSF to the extracellular domain of M-CSFR leads to dimerization of the receptor, which activates the cytoplasmic kinase domain, leading to autophosphorylation and phosphorylation of other cellular proteins (Hamilton J. A., J Leukoc Biol.,62(2):145-55 (1997); Hamilton J, A., Immuno Today., 18(7): 313-7(1997).

The full-length human M-CSF (also known as Colony stimulating factor or Colony stimulating factor 1 (CSF-1)) has a HUGO Gene Nomenclature Committee identifier number of HGNC:2432. See for example also the sequence available via the Uniprot reference P09603-1. M-CSF mRNA encodes a precursor protein of 554 amino acids. Through alternative mRNA splicing and differential post-translational proteolytic

processing, M-CSF can either be secreted into the circulation as a glycoprotein or chondroitin sulfate containing proteoglycan or be expressed as a membrane spanning glycoprotein on the surface of M-CSF producing cells. The three-dimensional structure of the bacterially expressed amino terminal 150 amino acids of human M-CSF, the minimal sequence required for full in vitro biological activity, indicates that this protein is a disulfide linked dimer with each monomer consisting of four alpha helical bundles and an anti-parallel beta sheet (Pandit et al., Science 258: 1358-62 (1992)). Three distinct M-CSF species are produced through alternative mRNA splicing. The three polypeptide precursors are M-CFSα of 256 amino acids, M-CSFβ of 554 amino acids, and M-CSFγ of 438 amino acids. M-CSFβ is a secreted protein that does not occur in a membrane-bound form. M-CSFα is expressed as an integral membrane protein that is slowly released by proteolytic cleavage. M-CSFα is cleaved at amino acids 191-197. The membrane-bound form of M-CSF can interact with receptors on nearby cells and therefore mediates specific cell-to-cell contacts. The term "M-CSF" may also include amino acids 36-438.

Anti-M-CSF antibodies that can be useful in the present invention include those anti-M-CSF antibodies disclosed in Publication No. WO 2005/068503, which is hereby incorporated by reference in its entirety for its teaching with respect to M-CSF antibodies. WO 2005/068503 discloses, for example, antibodies that bind the same epitopes as antibodies RX1, 5H4, MC1, and/or MC3, pharmaceutical formulations including an anti-M-CSF-specific antibody Human Engineered versions of the aforementioned antibodies, and methods of preparing the pharmaceutical formulations.

Other anti-M-CSF antibodies that can be useful in the present invention include those M-CSF antibodies disclosed in International Publication No. WO 2003/028752, US2009117103 and US2005059113, each of which is hereby incorporated by reference in its entirety for its teaching with respect to anti-M-CSF antibodies.

In one embodiment, the antibody or antigen binding fragment capable of binding to M-CSF useful in the methods of the invention includes an antibody that binds to a linear epitope represented by RFRDNTPN (SEQ ID NO: 1) or RFRDNTAN (SEQ ID NO: 2). Such an antibody is the human engineered RX1 (H-RX1) antibody disclosed in WO 2005/068503. In another embodiment, the antibody can be an antibody that binds to a linear epitope represented by ITFEFVDQE (SEQ ID NO: 3). Such an antibody is the 5H4 disclosed in WO 2005/068503.

In a preferred embodiment of the invention, the antibody or antigen binding fragment capable of binding to macrophage colony stimulating factor 1 (M-CSF) is MCS110 (lacnotuzumab). The heavy and light chains, variable regions, and complimentary determining regions (CDRs) of the MCS110 antibody or an antigen binding fragment thereof are shown in Table 1.

Table 1 : MCS110, an anti-M-CSF antibody

HC	QVQLQESGPGLVKPSQTLSLTCTVSDYSITSDYAWNWIRQFPG KGLEWMGYISYSGSTSYNPSLKSRITISRDTSKNQFSLQLNSVT AADTAVYYCASFDYAHAMDYWGQGTTVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK (SEQ ID NO: 4)
LC	DIVLTQSPAFLSVTPGEKVTFTCQASQSIGTSIHWYQQKTDQAP KLLIKYASESISGIPSRFSGSGSGTDFTLTISSVEAEDAADYYCQ QINSWPTTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 5)
Heavy Chain CDR1 (Kabat)	SDYAWN (SEQ ID NO: 6)
Heavy Chain CDR2 (Kabat)	YISYSGSTSYNPSLKS (SEQ ID NO: 7)
Heavy Chain CDR3 (Kabat)	FDYAHAMDY (SEQ ID NO: 8)
Light Chain CDR1 (Kabat)	QASQSIGTSIH (SEQ ID NO: 9)
Light Chain CDR2 (Kabat)	YASESIS (SEQ ID NO: 10)
Light Chain CDR3 (Kabat)	QQINSWPTT (SEQ ID NO: 11)

HC *(incl. leader peptide)*	*MGWSCIILFLVATATGVHS*QVQLQESGPGLVKPSQTLSLTCTVS DYSITSDYAWNWIRQFPGKGLEWMGYISYSGSTSYNPSLKSRI TISRDTSKNQFSLQLNSVTAADTAVYYCASFDYAHAMDYWGQ GTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 12)
LC *(including leader peptide)*	*MVSTPQFLVFLLFWIPASRG*DIVLTQSPAFLSVTPGEKVTFTCQ ASQSIGTSIHWYQQKTDQAPKLLIKYASESISGIPSRFSGSGSGT DFTLTISSVEAEDAADYYCQQINSWPTTFGGGTKLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC (SEQ ID NO: 13)
VL	DIVLTQSPAFLSVTPGEKVTFTCQASQSIGTSIHWYQQKTDQAP KLLIKYASESISGIPSRFSGSGSGTDFTLTISSVEAEDAADYYCQ QINSWPTTFGGGTKLEIK (SEQ ID NO: 14)
VH	QVQLQESGPGLVKPSQTLSLTCTVSDYSITSDYAWNWIRQFPG KGLEWMGYISYSGSTSYNPSLKSRITISRDTSKNQFSLQLNSVT AADTAVYYCASFDYAHAMDYWGQGTTVTVSS (SEQ ID NO: 15)

In one embodiment, the anti-M-CSF antibody or antigen binding fragment is a humanized antibody having the heavy chain variable region sequence set forth in SEQ ID NO: 15 and light chain variable region sequence set forth in SEQ ID NO: 14. In another embodiment, the anti-M-CSF antibody or antigen binding fragment comprises a heavy chain variable region that comprises CDR1, CDR2, and CDR3 domains; and a light chain variable region that comprises CDR1, CDR2, and CDR3 domains, wherein the heavy chain variable region CDR3 comprises the amino acids having the sequence set forth in SEQ ID NO:8; and a light chain variable region CDR3 comprises amino acids having the sequence set forth in SEQ ID NO:11; and wherein the antibody or antigen-binding portion thereof binds to human M-CSF. The antibody or antigen binding fragment

thereof can further include a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:7; and a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:10. The antibody or fragment thereof can further include a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:6; and a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:9.

In yet another example, the humanized antibody or human engineered antibody or antigen binding fragment thereof useful in the methods of the invention binds to human M-CSF, wherein said antibody binds an epitope of M-CSF that comprises RFRDNTPN (SEQ ID NO: 1) or RFRDNTAN (SEQ ID NO: 2), wherein said antibody has an affinity Kd (dissociation equilibrium constant) with respect to human M-CSF of at least 10^{-7} M, wherein said antibody comprises all three heavy chain CDRs as specified above.

The antibodies disclosed herein can be derivatives of single chain antibodies, diabodies, domain antibodies, nanobodies, and unibodies. For example, the invention provides an isolated monoclonal antibody (or a functional fragment thereof) comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence that is at least 90%, or preferably at least 95% identical to an amino acid sequence of SEQ ID NO: 15; the light chain variable region comprises an amino acid sequence that is at least 90%, or preferably at least 95% identical to an amino acid sequence of SEQ ID NO:14; and the antibody binds to M-CSF (*e.g.*, human and/or cynomologus M-CSF).

In other embodiments, the variable heavy chain (VH) and/or variable light chain (VL) amino acid sequences may be 95%, 96%, 97%, 98% or 99% identical to the sequences set forth in Table 1 above.

In certain embodiments, an antibody of the invention has a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein one or more of these CDR sequences have specified amino acid sequences based on the antibodies described herein or conservative modifications thereof, and wherein the antibodies retain the desired functional properties of the M-CSF-binding antibodies described in Table 1.

Accordingly, the invention provides an isolated M-CSF monoclonal antibody, or an antigen binding fragment thereof, comprising a heavy chain variable region comprising

CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein: the heavy chain variable region CDR1 amino acid sequence includes SEQ ID NO: 6, and conservative modifications thereof; the heavy chain variable region CDR2 amino acid sequences includes SEQ ID NO: 7 and conservative modifications thereof; the heavy chain variable region CDR3 amino acid sequences includes SEQ ID NO: 8 and conservative modifications thereof; the light chain variable regions CDR1 amino acid sequence includes SEQ ID NO: 9 and conservative modifications thereof; the light chain variable regions CDR2 amino acid sequences includes SEQ ID NO: 10 and conservative modifications thereof; the light chain variable regions of CDR3 amino acid sequence includes SEQ ID NO: 11, and conservative modifications thereof; and the antibody specifically binds to M-CSF.

The antibodies used in the invention can be fragment of an antibody that binds to M-CSF selected from the group consisting of; Fab, $F(ab_2)'$, $F(ab)_2'$, scFv, VHH, VH, VL and dAbs. Methods of producing M-CSF antibodies are described in WO 2005/068503.

Examples of PD-1 Inhibitors

In certain embodiments, the anti-M-CSF antibody is administered in combination with a PD-1 inhibitor. In some embodiments, the PD-1 inhibitor is chosen from Spartalizumab (PDR001), (Novartis), Nivolumab (Bristol-Myers Squibb), Pembrolizumab (Merck & Co), Pidilizumab (CureTech), MEDI0680 (Medimmune), REGN2810 (Regeneron), TSR-042 (Tesaro), PF-06801591 (Pfizer), BGB-A317 (Beigene), BGB-108 (Beigene), INCSHR1210 (Incyte), or AMP-224 (Amplimmune). In some embodiments, the PD-1 inhibitor is chosen from spartalizumab, nivolumab and pembrolizumab.

In one embodiment, the PD-1 inhibitor is an anti-PD-1 antibody or antigen binding fragment thereof. In a specific embodiment, the PD-1 inhibitor is an anti-PD-1 antibody as described in US 2015/0210769, published on July 30, 2015, entitled "Antibody Molecules to PD-1 and Uses Thereof," incorporated by reference in its entirety.

In one embodiment, the anti-PD-1 antibody or antigen binding fragment comprises at least one, two, three, four, five or six complementarity determining regions (CDRs) (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 2 (*e.g.*, from the heavy and light chain variable region sequences of BAP049-Clone-E or BAP049-Clone-B disclosed in Table 2), or encoded by a nucleotide sequence shown in Table 2. In some embodiments, the CDRs are according to the Kabat definition (*e.g.*, as set out in Table 2). In some embodiments,

the CDRs are according to the Chothia definition (*e.g.*, as set out in Table 2). In some embodiments, the CDRs are according to the combined CDR definitions of both Kabat and Chothia (*e.g.*, as set out in Table 2). In one embodiment, the combination of Kabat and Chothia CDR of VH CDR1 comprises the amino acid sequence GYTFTTYWMH (SEQ ID NO: 16). In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid substitutions (*e.g.,* conservative amino acid substitutions) or deletions, relative to an amino acid sequence shown in Table 2, or encoded by a nucleotide sequence shown in Table 2.

In one embodiment, the anti-PD-1 antibody or antigen binding fragment comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 37, a VHCDR2 amino acid sequence of SEQ ID NO: 38, and a VHCDR3 amino acid sequence of SEQ ID NO: 39; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 47, a VLCDR2 amino acid sequence of SEQ ID NO: 48, and a VLCDR3 amino acid sequence of SEQ ID NO: 49, each disclosed in Table 1.

In one embodiment, the antibody comprises a VH comprising a VHCDR1 encoded by the nucleotide sequence of SEQ ID NO: 69, a VHCDR2 encoded by the nucleotide sequence of SEQ ID NO: 70, and a VHCDR3 encoded by the nucleotide sequence of SEQ ID NO: 71; and a VL comprising a VLCDR1 encoded by the nucleotide sequence of SEQ ID NO: 75, a VLCDR2 encoded by the nucleotide sequence of SEQ ID NO: 76, and a VLCDR3 encoded by the nucleotide sequence of SEQ ID NO: 77, each disclosed in Table 1.

In one embodiment, the anti-PD-1 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 43, or an amino acid sequence at least 90%, 95%, or 99% identical or higher to SEQ ID NO: 43. In one embodiment, the anti-PD-1 antibody comprises a VL comprising the amino acid sequence of SEQ ID NO: 53, or an amino acid sequence at least 90%, 95%, or 99% identical or higher to SEQ ID NO: 53. In one embodiment, the anti-PD-1 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 43 and a VL comprising the amino acid sequence of SEQ ID NO: 53.

In one embodiment, the antibody comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 44, or a nucleotide sequence at least 90%, 95%, or 99% identical or

higher to SEQ ID NO: 44. In one embodiment, the antibody comprises a VL encoded by the nucleotide sequence of SEQ ID NO: 54, or a nucleotide sequence at least 90%, 95%, or 99% identical or higher to SEQ ID NO: 54. In one embodiment, the antibody comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 44 and a VL encoded by the nucleotide sequence of SEQ ID NO: 54.

In one embodiment, the anti-PD-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 45, or an amino acid sequence at least 90%, 95%, or 99% identical or higher to SEQ ID NO: 45. In one embodiment, the anti-PD-1 antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 55, or an amino acid sequence at least 90%, 95%, or 99% identical or higher to SEQ ID NO: 55. In one embodiment, the anti-PD-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 45 and a light chain comprising the amino acid sequence of SEQ ID NO: 55. In one embodiment, the anti-PD-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 45 and a light chain comprising the amino acid sequence of SEQ ID NO: 55.

In one embodiment, the antibody comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 46, or a nucleotide sequence at least 90%, 95%, or 99% identical or higher to SEQ ID NO: 46. In one embodiment, the antibody comprises a light chain encoded by the nucleotide sequence of SEQ ID NO: 56, or a nucleotide sequence at least 90%, 95%, or 99% identical or higher to SEQ ID NO: 56. In one embodiment, the antibody comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 46 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 56.

The antibodies described herein can be made by vectors, host cells, and methods described in US 2015/0210769, incorporated by reference in its entirety.

Table 2. Amino acid and nucleotide sequences of exemplary anti-PD-1 antibodies

BAP049-Clone-B HC		
SEQ ID NO: 17 (Kabat)	HCDR1	TYWMH
SEQ ID NO: 18 (Kabat)	HCDR2	NIYPGTGGSNFDEKFKN
SEQ ID NO: 19 (Kabat)	HCDR3	WTTGTGAY
SEQ ID NO: 20 (Chothia)	HCDR1	GYTFTTY

SEQ ID NO: 21 (Chothia)	HCDR2	YPGTGG
SEQ ID NO: 22 (Chothia)	HCDR3	WTTGTGAY
SEQ ID NO: 23	VH	EVQLVQSGAEVKKPGESLRISCKGSGYTFTTY WMHWVRQATGQGLEWMGNIYPGTGGSNFDE KFKNRVTITADKSTSTAYMELSSLRSEDTAVYY CTRWTTGTGAYWGQGTTVTVSS
SEQ ID NO: 24	DNA VH	GAGGTGCAGCTGGTGCAGTCAGGCGCCGAA GTGAAGAAGCCCGGCGAGTCACTGAGAATT AGCTGTAAAGGTTCAGGCTACACCTTCACTA CCTACTGGATGCACTGGGTCCGCCAGGCTA CCGGTCAAGGCCTCGAGTGGATGGGTAATA TCTACCCCGGCACCGGCGGCTCTAACTTCG ACGAGAAGTTTAAGAATAGAGTGACTATCAC CGCCGATAAGTCTACTAGCACCGCCTATATG GAACTGTCTAGCCTGAGATCAGAGGACACC GCCGTCTACTACTGCACTAGGTGGACTACCG GCACAGGCGCCTACTGGGGTCAAGGCACTA CCGTGACCGTGTCTAGC
SEQ ID NO: 25	Heavy chain	EVQLVQSGAEVKKPGESLRISCKGSGYTFTTY WMHWVRQATGQGLEWMGNIYPGTGGSNFDE KFKNRVTITADKSTSTAYMELSSLRSEDTAVYY CTRWTTGTGAYWGQGTTVTVSSASTKGPSVF PLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTKTYTCNVDHKPSNTKVDKRVESKYGPP CPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLG
SEQ ID NO: 26	DNA heavy chain	GAGGTGCAGCTGGTGCAGTCAGGCGCCGAA GTGAAGAAGCCCGGCGAGTCACTGAGAATT AGCTGTAAAGGTTCAGGCTACACCTTCACTA CCTACTGGATGCACTGGGTCCGCCAGGCTA CCGGTCAAGGCCTCGAGTGGATGGGTAATA TCTACCCCGGCACCGGCGGCTCTAACTTCG ACGAGAAGTTTAAGAATAGAGTGACTATCAC CGCCGATAAGTCTACTAGCACCGCCTATATG GAACTGTCTAGCCTGAGATCAGAGGACACC GCCGTCTACTACTGCACTAGGTGGACTACCG GCACAGGCGCCTACTGGGGTCAAGGCACTA CCGTGACCGTGTCTAGCGCTAGCACTAAGG GCCCGTCCGTGTTCCCCCTGGCACCTTGTA

		GCCGGAGCACTAGCGAATCCACCGCTGCCC TCGGCTGCCTGGTCAAGGATTACTTCCCGGA GCCCGTGACCGTGTCCTGGAACAGCGGAGC CCTGACCTCCGGAGTGCACACCTTCCCCGC TGTGCTGCAGAGCTCCGGGCTGTACTCGCT GTCGTCGGTGGTCACGGTGCCTTCATCTAGC CTGGGTACCAAGACCTACACTTGCAACGTGG ACCACAAGCCTTCCAACACTAAGGTGGACAA GCGCGTCGAATCGAAGTACGGCCCACCGTG CCCGCCTTGTCCCGCGCCGGAGTTCCTCGG CGGTCCCTCGGTCTTTCTGTTCCCACCGAAG CCCAAGGACACTTTGATGATTTCCCGCACCC CTGAAGTGACATGCGTGGTCGTGGACGTGT CACAGGAAGATCCGGAGGTGCAGTTCAATTG GTACGTGGATGGCGTCGAGGTGCACAACGC CAAAACCAAGCCGAGGGAGGAGCAGTTCAA CTCCACTTACCGCGTCGTGTCCGTGCTGACG GTGCTGCATCAGGACTGGCTGAACGGGAAG GAGTACAAGTGCAAAGTGTCCAACAAGGGAC TTCCTAGCTCAATCGAAAAGACCATCTCGAA AGCCAAGGGACAGCCCCGGGAACCCCAAGT GTATACCCTGCCACCGAGCCAGGAAGAAAT GACTAAGAACCAAGTCTCATTGACTTGCCTT GTGAAGGGCTTCTACCCATCGGATATCGCCG TGGAATGGGAGTCCAACGGCCAGCCGGAAA ACAACTACAAGACCACCCCTCCGGTGCTGGA CTCAGACGGATCCTTCTTCCTCTACTCGCGG CTGACCGTGGATAAGAGCAGATGGCAGGAG GGAAATGTGTTCAGCTGTTCTGTGATGCATG AAGCCCTGCACAACCACTACACTCAGAAGTC CCTGTCCCTCTCCCTGGGA
BAP049-Clone-B LC		
SEQ ID NO: 27 (Kabat)	LCDR1	KSSQSLLDSGNQKNFLT
SEQ ID NO: 28 (Kabat)	LCDR2	WASTRES
SEQ ID NO: 29 (Kabat)	LCDR3	QNDYSYPYT
SEQ ID NO: 30 (Chothia)	LCDR1	SQSLLDSGNQKNF
SEQ ID NO: 31 (Chothia)	LCDR2	WAS
SEQ ID NO: 32 (Chothia)	LCDR3	DYSYPY
SEQ ID NO: 33	VL	EIVLTQSPATLSLSPGERATLSCKSSQSLLDSG NQKNFLTWYQQKPGKAPKLLIYWASTRESGVP

		SRFSGSGSGTDFTFTISSLQPEDIATYYCQNDY SYPYTFGQGTKVEIK
SEQ ID NO: 34	DNA VL	GAGATCGTCCTGACTCAGTCACCCGCTACCC TGAGCCTGAGCCCTGGCGAGCGGGCTACAC TGAGCTGTAAATCTAGTCAGTCACTGCTGGA TAGCGGTAATCAGAAGAACTTCCTGACCTGG TATCAGCAGAAGCCCGGTAAAGCCCCTAAGC TGCTGATCTACTGGGCCTCTACTAGAGAATC AGGCGTGCCCTCTAGGTTTAGCGGTAGCGG TAGTGGCACCGACTTCACCTTCACTATCTCT AGCCTGCAGCCCGAGGATATCGCTACCTACT ACTGTCAGAACGACTATAGCTACCCCTACAC CTTCGGTCAAGGCACTAAGGTCGAGATTAAG
SEQ ID NO: 35	Light chain	EIVLTQSPATLSLSPGERATLSCKSSQSLLDSG NQKNFLTWYQQKPGKAPKLLIYWASTRESGVP SRFSGSGSGTDFTFTISSLQPEDIATYYCQNDY SYPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 36	DNA light chain	GAGATCGTCCTGACTCAGTCACCCGCTACCC TGAGCCTGAGCCCTGGCGAGCGGGCTACAC TGAGCTGTAAATCTAGTCAGTCACTGCTGGA TAGCGGTAATCAGAAGAACTTCCTGACCTGG TATCAGCAGAAGCCCGGTAAAGCCCCTAAGC TGCTGATCTACTGGGCCTCTACTAGAGAATC AGGCGTGCCCTCTAGGTTTAGCGGTAGCGG TAGTGGCACCGACTTCACCTTCACTATCTCT AGCCTGCAGCCCGAGGATATCGCTACCTACT ACTGTCAGAACGACTATAGCTACCCCTACAC CTTCGGTCAAGGCACTAAGGTCGAGATTAAG CGTACGGTGGCCGCTCCCAGCGTGTTCATC TTCCCCCCCAGCGACGAGCAGCTGAAGAGC GGCACCGCCAGCGTGGTGTGCCTGCTGAAC AACTTCTACCCCCGGGAGGCCAAGGTGCAG TGGAAGGTGGACAACGCCCTGCAGAGCGGC AACAGCCAGGAGAGCGTCACCGAGCAGGAC AGCAAGGACTCCACCTACAGCCTGAGCAGC ACCCTGACCCTGAGCAAGGCCGACTACGAG AAGCATAAGGTGTACGCCTGCGAGGTGACC CACCAGGGCCTGTCCAGCCCCGTGACCAAG AGCTTCAACAGGGGCGAGTGC
BAP049-Clone-E HC		
SEQ ID NO: 37 (Kabat)	HCDR1	TYWMH
SEQ ID NO: 38 (Kabat)	HCDR2	NIYPGTGGSNFDEKFKN

SEQ ID NO: 39 (Kabat)	HCDR3	WTTGTGAY
SEQ ID NO: 40 (Chothia)	HCDR1	GYTFTTY
SEQ ID NO: 41 (Chothia)	HCDR2	YPGTGG
SEQ ID NO: 42 (Chothia)	HCDR3	WTTGTGAY
SEQ ID NO: 43	VH	EVQLVQSGAEVKKPGESLRISCKGSGYTFTTY WMHWVRQATGQGLEWMGNIYPGTGGSNFDE KFKNRVTITADKSTSTAYMELSSLRSEDTAVYY CTRWTTGTGAYWGQGTTVTVSS
SEQ ID NO: 44	DNA VH	GAGGTGCAGCTGGTGCAGTCAGGCGCCGAA GTGAAGAAGCCCGGCGAGTCACTGAGAATT AGCTGTAAAGGTTCAGGCTACACCTTCACTA CCTACTGGATGCACTGGGTCCGCCAGGCTA CCGGTCAAGGCCTCGAGTGGATGGGTAATA TCTACCCCGGCACCGGCGGCTCTAACTTCG ACGAGAAGTTTAAGAATAGAGTGACTATCAC CGCCGATAAGTCTACTAGCACCGCCTATATG GAACTGTCTAGCCTGAGATCAGAGGACACC GCCGTCTACTACTGCACTAGGTGGACTACCG GCACAGGCGCCTACTGGGGTCAAGGCACTA CCGTGACCGTGTCTAGC
SEQ ID NO: 45	Heavy chain	EVQLVQSGAEVKKPGESLRISCKGSGYTFTTY WMHWVRQATGQGLEWMGNIYPGTGGSNFDE KFKNRVTITADKSTSTAYMELSSLRSEDTAVYY CTRWTTGTGAYWGQGTTVTVSSASTKGPSVF PLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTKTYTCNVDHKPSNTKVDKRVESKYGPP CPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLG
SEQ ID NO: 46	DNA heavy chain	GAGGTGCAGCTGGTGCAGTCAGGCGCCGAA GTGAAGAAGCCCGGCGAGTCACTGAGAATT AGCTGTAAAGGTTCAGGCTACACCTTCACTA CCTACTGGATGCACTGGGTCCGCCAGGCTA CCGGTCAAGGCCTCGAGTGGATGGGTAATA TCTACCCCGGCACCGGCGGCTCTAACTTCG ACGAGAAGTTTAAGAATAGAGTGACTATCAC CGCCGATAAGTCTACTAGCACCGCCTATATG GAACTGTCTAGCCTGAGATCAGAGGACACC

		GCCGTCTACTACTGCACTAGGTGGACTACCG GCACAGGCGCCTACTGGGGTCAAGGCACTA CCGTGACCGTGTCTAGCGCTAGCACTAAGG GCCCGTCCGTGTTCCCCCTGGCACCTTGTA GCCGGAGCACTAGCGAATCCACCGCTGCCC TCGGCTGCCTGGTCAAGGATTACTTCCCGGA GCCCGTGACCGTGTCCTGGAACAGCGGAGC CCTGACCTCCGGAGTGCACACCTTCCCCGC TGTGCTGCAGAGCTCCGGGCTGTACTCGCT GTCGTCGGTGGTCACGGTGCCTTCATCTAGC CTGGGTACCAAGACCTACACTTGCAACGTGG ACCACAAGCCTTCCAACACTAAGGTGGACAA GCGCGTCGAATCGAAGTACGGCCCACCGTG CCCGCCTTGTCCCGCGCCGGAGTTCCTCGG CGGTCCCTCGGTCTTTCTGTTCCCACCGAAG CCCAAGGACACTTTGATGATTTCCCGCACCC CTGAAGTGACATGCGTGGTCGTGGACGTGT CACAGGAAGATCCGGAGGTGCAGTTCAATTG GTACGTGGATGGCGTCGAGGTGCACAACGC CAAAACCAAGCCGAGGGAGGAGCAGTTCAA CTCCACTTACCGCGTCGTGTCCGTGCTGACG GTGCTGCATCAGGACTGGCTGAACGGGAAG GAGTACAAGTGCAAAGTGTCCAACAAGGGAC TTCCTAGCTCAATCGAAAAGACCATCTCGAA AGCCAAGGGACAGCCCCGGGAACCCCAAGT GTATACCCTGCCACCGAGCCAGGAAGAAAT GACTAAGAACCAAGTCTCATTGACTTGCCTT GTGAAGGGCTTCTACCCATCGGATATCGCCG TGGAATGGGAGTCCAACGGCCAGCCGGAAA ACAACTACAAGACCACCCCTCCGGTGCTGGA CTCAGACGGATCCTTCTTCCTCTACTCGCGG CTGACCGTGGATAAGAGCAGATGGCAGGAG GGAAATGTGTTCAGCTGTTCTGTGATGCATG AAGCCCTGCACAACCACTACACTCAGAAGTC CCTGTCCCTCTCCCTGGGA
BAP049-Clone-E LC		
SEQ ID NO: 47 (Kabat)	LCDR1	KSSQSLLDSGNQKNFLT
SEQ ID NO: 48 (Kabat)	LCDR2	WASTRES
SEQ ID NO: 49 (Kabat)	LCDR3	QNDYSYPYT
SEQ ID NO: 50 (Chothia)	LCDR1	SQSLLDSGNQKNF
SEQ ID NO: 51 (Chothia)	LCDR2	WAS

SEQ ID NO: 52 (Chothia)	LCDR3	DYSYPY
SEQ ID NO: 53	VL	EIVLTQSPATLSLSPGERATLSCKSSQSLLDSG NQKNFLTWYQQKPGQAPRLLIYWASTRESGV PSRFSGSGSGTDFTFTISSLEAEDAATYYCQN DYSYPYTFGQGTKVEIK
SEQ ID NO: 54	DNA VL	GAGATCGTCCTGACTCAGTCACCCGCTACCC TGAGCCTGAGCCCTGGCGAGCGGGCTACAC TGAGCTGTAAATCTAGTCAGTCACTGCTGGA TAGCGGTAATCAGAAGAACTTCCTGACCTGG TATCAGCAGAAGCCCGGTCAAGCCCCTAGA CTGCTGATCTACTGGGCCTCTACTAGAGAAT CAGGCGTGCCCTCTAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCTTCACTATCTC TAGCCTGGAAGCCGAGGACGCCGCTACCTA CTACTGTCAGAACGACTATAGCTACCCCTAC ACCTTCGGTCAAGGCACTAAGGTCGAGATTA AG
SEQ ID NO: 55	Light chain	EIVLTQSPATLSLSPGERATLSCKSSQSLLDSG NQKNFLTWYQQKPGQAPRLLIYWASTRESGV PSRFSGSGSGTDFTFTISSLEAEDAATYYCQN DYSYPYTFGQGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 56	DNA light chain	GAGATCGTCCTGACTCAGTCACCCGCTACCC TGAGCCTGAGCCCTGGCGAGCGGGCTACAC TGAGCTGTAAATCTAGTCAGTCACTGCTGGA TAGCGGTAATCAGAAGAACTTCCTGACCTGG TATCAGCAGAAGCCCGGTCAAGCCCCTAGA CTGCTGATCTACTGGGCCTCTACTAGAGAAT CAGGCGTGCCCTCTAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCTTCACTATCTC TAGCCTGGAAGCCGAGGACGCCGCTACCTA CTACTGTCAGAACGACTATAGCTACCCCTAC ACCTTCGGTCAAGGCACTAAGGTCGAGATTA AGCGTACGGTGGCCGCTCCCAGCGTGTTCA TCTTCCCCCCCAGCGACGAGCAGCTGAAGA GCGGCACCGCCAGCGTGGTGTGCCTGCTGA ACAACTTCTACCCCCGGGAGGCCAAGGTGC AGTGGAAGGTGGACAACGCCCTGCAGAGCG GCAACAGCCAGGAGAGCGTCACCGAGCAGG ACAGCAAGGACTCCACCTACAGCCTGAGCA GCACCCTGACCCTGAGCAAGGCCGACTACG AGAAGCATAAGGTGTACGCCTGCGAGGTGA CCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACAGGGGCGAGTGC

BAP049-Clone-B HC		
SEQ ID NO: 57 (Kabat)	HCDR1	ACCTACTGGATGCAC
SEQ ID NO: 58 (Kabat)	HCDR2	AATATCTACCCCGGCACCGGCGGCTCTAACT TCGACGAGAAGTTTAAGAAT
SEQ ID NO: 59 (Kabat)	HCDR3	TGGACTACCGGCACAGGCGCCTAC
SEQ ID NO: 60 (Chothia)	HCDR1	GGCTACACCTTCACTACCTAC
SEQ ID NO: 61 (Chothia)	HCDR2	TACCCCGGCACCGGCGGC
SEQ ID NO: 62 (Chothia)	HCDR3	TGGACTACCGGCACAGGCGCCTAC
BAP049-Clone-B LC		
SEQ ID NO: 63 (Kabat)	LCDR1	AAATCTAGTCAGTCACTGCTGGATAGCGGTA ATCAGAAGAACTTCCTGACC
SEQ ID NO: 64 (Kabat)	LCDR2	TGGGCCTCTACTAGAGAATCA
SEQ ID NO: 65 (Kabat)	LCDR3	CAGAACGACTATAGCTACCCCTACACC
SEQ ID NO: 66 (Chothia)	LCDR1	AGTCAGTCACTGCTGGATAGCGGTAATCAGA AGAACTTC
SEQ ID NO: 67 (Chothia)	LCDR2	TGGGCCTCT
SEQ ID NO: 68 (Chothia)	LCDR3	GACTATAGCTACCCCTAC
BAP049-Clone-E HC		
SEQ ID NO: 69 (Kabat)	HCDR1	ACCTACTGGATGCAC
SEQ ID NO: 70 (Kabat)	HCDR2	AATATCTACCCCGGCACCGGCGGCTCTAACT TCGACGAGAAGTTTAAGAAT
SEQ ID NO: 71 (Kabat)	HCDR3	TGGACTACCGGCACAGGCGCCTAC
SEQ ID NO: 72 (Chothia)	HCDR1	GGCTACACCTTCACTACCTAC
SEQ ID NO: 73 (Chothia)	HCDR2	TACCCCGGCACCGGCGGC
SEQ ID NO: 74 (Chothia)	HCDR3	TGGACTACCGGCACAGGCGCCTAC
BAP049-Clone-E LC		
SEQ ID NO: 75 (Kabat)	LCDR1	AAATCTAGTCAGTCACTGCTGGATAGCGGTA ATCAGAAGAACTTCCTGACC
SEQ ID NO: 76 (Kabat)	LCDR2	TGGGCCTCTACTAGAGAATCA
SEQ ID NO: 77 (Kabat)	LCDR3	CAGAACGACTATAGCTACCCCTACACC

SEQ ID NO: 78 (Chothia)	LCDR1	AGTCAGTCACTGCTGGATAGCGGTAATCAGA AGAACTTC
SEQ ID NO: 79 (Chothia)	LCDR2	TGGGCCTCT
SEQ ID NO: 80 (Chothia)	LCDR3	GACTATAGCTACCCCTAC

Table 3. Amino acid sequences of the heavy and light chain leader sequences for humanized mAbs BAP049-Clone-B and BAP049-Clone-E

BAP049-Clone-B SEQ ID NO: 81	HC	MAWVWTLPFLMAAAQSVQA
SEQ ID NO: 82	LC	MSVLTQVLALLLLWLTGTRC
BAP049-Clone-E SEQ ID NO: 83	HC	MAWVWTLPFLMAAAQSVQA
SEQ ID NO: 84	LC	MSVLTQVLALLLLWLTGTRC

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Table 4. Constant region amino acid sequences of human IgG heavy chains and human kappa light chain

HC SEQ ID NO: 85	IgG4 (S228P) mutant constant region amino acid sequence (EU Numbering) ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLGK
LC SEQ ID NO: 86	Human kappa constant region amino acid sequence

	RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC
HC SEQ ID NO: 87	IgG4 (S228P) mutant constant region amino acid sequence lacing C-terminal lysine (K) (EU Numbering) ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLG
HC SEQ ID NO: 88	IgG1 wild type ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
HC SEQ ID NO: 89	IgG1 (N297A) mutant constant region amino acid sequence (EU Numbering) ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK

HC SEQ ID NO: 90	IgG1 (D265A, P329A) mutant constant region amino acid sequence (EU Numbering) ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVAVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LAAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
HC SEQ ID NO: 91	IgG1 (L234A, L235A) mutant constant region amino acid sequence (EU Numbering) ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPEAAGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK

Other Exemplary PD-1 Inhibitors

In one embodiment, the anti-PD-1 antibody or antigen binding fragment is Nivolumab (Bristol-Myers Squibb), also known as MDX-1106, MDX-1106-04, ONO-4538, BMS-936558, or OPDIVO®. Nivolumab (clone 5C4) and other anti-PD-1 antibodies are disclosed in US 8,008,449 and WO 2006/121168, incorporated by reference in their entirety. In one embodiment, the anti-PD-1 antibody or antigen binding fragment comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of Nivolumab, *e.g.*, as disclosed in Table 5.

In one embodiment, the anti-PD-1 antibody or antigen binding fragment is Pembrolizumab (Merck & Co), also known as Lambrolizumab, MK-3475, MK03475, SCH-900475, or KEYTRUDA®. Pembrolizumab and other anti-PD-1 antibodies are disclosed in Hamid, O. *et al.* (2013) *New England Journal of Medicine* 369 (2): 134–44,

US 8,354,509, and WO 2009/114335, incorporated by reference in their entirety. In one embodiment, the anti-PD-1 antibody or antigen binding fragment comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of Pembrolizumab, *e.g.*, as disclosed in Table 5.

In one embodiment, the anti-PD-1 antibody or antigen binding fragment is Pidilizumab (CureTech), also known as CT-011. Pidilizumab and other anti-PD-1 antibodies are disclosed in Rosenblatt, J. *et al.* (2011) *J Immunotherapy* 34(5): 409-18, US 7,695,715, US 7,332,582, and US 8,686,119, incorporated by reference in their entirety. In one embodiment, the anti-PD-1 antibody or antigen binding fragment comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of Pidilizumab, *e.g.*, as disclosed in Table 5.

In one embodiment, the anti-PD-1 antibody or antigen binding fragment is MEDI0680 (Medimmune), also known as AMP-514. MEDI0680 and other anti-PD-1 antibodies are disclosed in US 9,205,148 and WO 2012/145493, incorporated by reference in their entirety. In one embodiment, the anti-PD-1 antibody or antigen binding fragment comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of MEDI0680.

In one embodiment, the anti-PD-1 antibody is REGN2810 (Regeneron). In one embodiment, the anti-PD-1 antibody or antigen binding fragment comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of REGN2810.

In one embodiment, the anti-PD-1 antibody or antigen binding fragment is PF-06801591 (Pfizer). In one embodiment, the anti-PD-1 antibody or antigen binding fragment comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of PF-06801591.

In one embodiment, the anti-PD-1 antibody or antigen binding fragment is BGB-A317 or BGB-108 (Beigene). In one embodiment, the anti-PD-1 antibody or antigen binding

fragment comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of BGB-A317 or BGB-108.

In one embodiment, the anti-PD-1 antibody or antigen binding fragment is INCSHR1210 (Incyte), also known as INCSHR01210 or SHR-1210. In one embodiment, the anti-PD-1 antibody or antigen binding fragment comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of INCSHR1210.

In one embodiment, the anti-PD-1 antibody or antigen binding fragment is TSR-042 (Tesaro), also known as ANB011. In one embodiment, the anti-PD-1 antibody or antigen binding fragment comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of TSR-042.

Further known anti-PD-1 antibodies include those described, *e.g.*, in WO 2015/112800, WO 2016/092419, WO 2015/085847, WO 2014/179664, WO 2014/194302, WO 2014/209804, WO 2015/200119, US 8,735,553, US 7,488,802, US 8,927,697, US 8,993,731, and US 9,102,727, incorporated by reference in their entirety.

In one embodiment, the anti-PD-1 antibody or antigen binding fragment is an antibody that competes for binding with, and/or binds to the same epitope on PD-1 as, one of the anti-PD-1 antibodies described herein.

In one embodiment, the PD-1 inhibitor is a peptide that inhibits the PD-1 signaling pathway, *e.g.*, as described in US 8,907,053, incorporated by reference in its entirety. In one embodiment, the PD-1 inhibitor is an immunoadhesin (*e.g.*, an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region (*e.g.*, an Fc region of an immunoglobulin sequence). In one embodiment, the PD-1 inhibitor is AMP-224 (B7-DCIg (Amplimmune), *e.g.*, disclosed in WO 2010/027827 and WO 2011/066342, incorporated by reference in their entirety).

Table 5. Amino acid sequences of other exemplary anti-PD-1 antibodies

Nivolumab	
SEQ ID NO: 92 Heavy chain	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAP GKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNTLFLQM

	NSLRAEDTAVYYCATNDDYWGQGTLVTVSSASTKGPSVFPLA PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSC SVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 93 Light chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQ APRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVY YCQQSSNWPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC
Pembrolizumab	
SEQ ID NO: 94 Heavy chain	QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAP GQGLEWMGGINPSNGGTNFNEKFKNRVTLTTDSSTTTAYME LKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAST KGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHK PSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 95 Light chain	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQ KPGQAPRLLIYLASYLESGVPARFSGSGSGTDFTLTISSLEPE DFAVYYCQHSRDLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC
Pidilizumab	
SEQ ID NO: 96 Heavy chain	QVQLVQSGSELKKPGASVKISCKASGYTFTNYGMNWVRQAP GQGLQWMGWINTDSGESTYAEEFKGRFVFSLDTSVNTAYLQI TSLTAEDTGMYFCVRVGYDALDYWGQGTLVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 97 Light chain	EIVLTQSPSSLSASVGDRVTITCSARSSVSYMHWFQQKPGKA PKLWIYRTSNLASGVPSRFSGSGSGTSYCLTINSLQPEDFATY

	YCQQRSSFPLTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC

Gemcitibine

Gemcitabine, used as the hydrochloride salt is also known as 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (beta-isomer) or alternatively 4-amino-1-[(2R,4R,5R)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]pyrimidin-2-one. The CAS ID is 95058-81-4. It is widely available and is sold for example under the brand name Gemzar (Eli Lilly), as well as in generic versions. Gemcitabine and a process for its preparation is disclosed in US4808614, which is incorporated by reference in its entirety. Gemcitabine is a chemotherapy medication used in the treatment of some cancers and functions as a pyrimidine antagonist. Gemcitabine is thought to kill cells undergoing DNA synthesis and block the progression of cells through the G1/S-phase boundary. Gemcitabine is thought to be metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate has been shown to inhibit ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. Gemcitabine triphosphate has been shown to compete with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP by the action of the diphosphate enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands, which eventually is thought to result in the initiation of apoptotic cell death.

Paclitaxel

Paclitaxel, also known as (2α,4α,5β,7β,10β,13α)-4,10-Bis(acetyloxy)-13-{[(2R,3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoyl]oxy}-1,7-dihydroxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate, is widely available and is sold under the brand name Taxol among others. Paclitaxel and methods for its preparations are disclosed in U.S. Patent US5760072. Paclitaxel is a chemotherapy medication used in the treatment of some cancers and is thought to function as a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic

cellular functions. Paclitaxel is thought to induce abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Nab-paclitaxel

Nab-paclitaxel relates to paclitaxel bound to albumin nano-particles (protein bound paclitaxel) and is widely available and sold under the brand name Abraxane (Celgene). It is disclosed in US7820788, US7923536, US8138229 and US8853260, which are incorporated by reference in their entirety. Nab-Paclitaxel is thought to utilise the natural properties of albumin to reversibly bind paclitaxel, transport it across the endothelial cell and concentrate it in areas of tumour. The proposed mechanism of drug delivery involves, in part, glycoprotein 60-mediated endothelial cell transcytosis of paclitaxel-bound albumin and accumulation in the area of tumour by albumin binding to SPARC (secreted protein, acidic and rich in cysteine). Clinical studies have shown that nab-paclitaxel is significantly more effective than paclitaxel formulated as Cremophor EL (CrEL, Taxol, CrEL-paclitaxel), see Gradishar WJ.Albumin-bound paclitaxel: A Next-Generation Taxane. Expert Opin Pharmacother. 2006 Jun;7(8):1041-53.

Compositions

The present disclosure relates to a pharmaceutical product or a commercial package comprising a combination product comprising, an antibody or antigen binding fragment capable of binding to M-CSF (such as lacnotuzumab), and at least one or more of gemcitabine, nab-paclitaxel and a PD-1 inhibitor (such as spartalizumab) in particular together with instructions for simultaneous, separate or sequential use (especially for being jointly active) thereof in the treatment of cancer.

In one aspect, the present invention provides compositions, *e.g.*, pharmaceutically acceptable compositions, which include an M-CSF antibody or antigen binding fragment as described herein and optionally a PD-1 antibody or antigen binding fragment as described herein and, formulated together with a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, isotonic and absorption delaying agents, and the like that are physiologically compatible. The carrier can be suitable for intravenous, intramuscular, subcutaneous, parenteral, rectal, spinal or epidermal administration (*e.g.* by injection or infusion).

The compositions of this invention may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.*,

injectable and infusible solutions), dispersions or suspensions, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions. The preferred mode of administration is parenteral (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular). In a preferred embodiment, the combination disclosed herein is administered by intravenous infusion or injection. In another preferred embodiment, the combination disclosed herein is administered by intramuscular or subcutaneous injection.

Therapeutic compositions typically should be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high antibody concentration. Sterile injectable solutions can be prepared by incorporating the active compound (*i.e.,* antibody or antibody portion) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

Pharmaceutical compositions for use in the disclosed methods may be manufactured in conventional manner. The use of antibodies as the active ingredient of pharmaceuticals is now widespread, including the products Herceptin® (trastuzumab), Rituxan® (rituximab), Synagis® (palivizumab), etc. Techniques for lyophilisation, preparation of aqueous formulations, and purification of antibodies to a pharmaceutical grade are well known in the art.

Antibodies are typically formulated either in aqueous form ready for parenteral administration or as lyophilisates for reconstitution with a suitable diluent prior to administration. In some embodiments of the disclosed methods and uses, the antibodies

of the present invention are formulated as a lyophilisate. Suitable lyophilisate formulations can be reconstituted in a small liquid volume (e.g., 2 ml or less) to allow subcutaneous administration and can provide solutions with low levels of antibody aggregation. For immediate administration, it is dissolved in a suitable aqueous carrier, for example sterile water for injection or sterile buffered physiological saline. If it is considered desirable to make up a solution of larger volume for administration by infusion rather than a bolus injection, may be advantageous to incorporate human serum albumin or the patient's own heparinised blood into the saline at the time of formulation. The presence of an excess of such physiologically inert protein prevents loss of antibody by adsorption onto the walls of the container and tubing used with the infusion solution.

The anti-M-CSF antibodies described herein can be formulated into a formulation (*e.g.,* a dose formulation or dosage form) suitable for administration (*e.g.,* intravenous administration) to a subject as described herein. The formulation described herein can be a liquid formulation, a lyophilized formulation, or a reconstituted formulation.

In certain embodiments, the formulation is a liquid formulation. In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-M-CSF antibody (*e.g.*, an anti-M-CSF antibody described herein) and a buffering agent.

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-M-CSF antibody present at a concentration of 25 mg/mL to 250 mg/mL, *e.g.,* 50 mg/mL to 200 mg/mL, 60 mg/mL to 180 mg/mL, 70 mg/mL to 150 mg/mL, 80 mg/mL to 120 mg/mL, 90 mg/mL to 110 mg/mL, 50 mg/mL to 150 mg/mL, 50 mg/mL to 100 mg/mL, 150 mg/mL to 200 mg/mL, or 100 mg/mL to 200 mg/mL, *e.g.,* 50 mg/mL, 60 mg/mL, 70 mg/mL, 80 mg/mL, 90 mg/mL, 100 mg/mL, 110 mg/mL, 120 mg/mL, 130 mg/mL, 140 mg/mL, or 150 mg/mL. In certain embodiments, the anti-M-CSF antibody is present at a concentration of 80 mg/mL to 120 mg/mL, *e.g.,* 100 mg/mL.

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises a buffering agent comprising histidine (*e.g.,* a histidine buffer). In certain embodiments, the buffering agent (*e.g.,* histidine buffer) is present at a concentration of 1 mM to 100 mM, *e.g.*, 2 mM to 50 mM, 5 mM to 40 mM, 10 mM to 30 mM, 15 to 25 mM, 5 mM to 40 mM, 5 mM to 30 mM, 5 mM to 20 mM, 5 mM to 10 mM, 40 mM to 50 mM, 30 mM to 50 mM, 20 mM to 50 mM, 10 mM to 50 mM, or 5 mM to 50 mM, *e.g.,* 2 mM, 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM, or 50 mM. In some embodiments, the buffering agent (*e.g.*, histidine buffer) is present at a concentration of 15 mM to 25 mM, *e.g.,* 20

mM. In other embodiments, the buffering agent (*e.g.,* a histidine buffer) or the formulation has a pH of 4 to 7, *e.g.,* 5 to 6, *e.g.,* 5, 5.5, or 6. In some embodiments, the buffering agent (*e.g.,* histidine buffer) or the formulation has a pH of 5 to 6, *e.g.,* 5.5. In certain embodiments, the buffering agent comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM) and has a pH of 5 to 6 (*e.g.,* 5.5). In certain embodiments, the buffering agent comprises histidine and histidine-HCl.

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-M-CSF antibody present at a concentration of 80 to 120 mg/mL, *e.g.,* 100 mg/mL; and a buffering agent that comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM), at a pH of 5 to 6 (*e.g.,* 5.5).

In some embodiments, the formulation (*e.g.*, liquid formulation) further comprises a carbohydrate. In certain embodiments, the carbohydrate is sucrose. In some embodiments, the carbohydrate (*e.g.,* sucrose) is present at a concentration of 50 mM to 500 mM, *e.g.,* 100 mM to 400 mM, 150 mM to 300 mM, 180 mM to 250 mM, 200 mM to 240 mM, 210 mM to 230 mM, 100 mM to 300 mM, 100 mM to 250 mM, 100 mM to 200 mM, 100 mM to 150 mM, 300 mM to 400 mM, 200 mM to 400 mM, or 100 mM to 400 mM, *e.g.,* 100 mM, 150 mM, 180 mM, 200 mM, 220 mM, 250 mM, 300 mM, 350 mM, or 400 mM. In some embodiments, the formulation comprises a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, *e.g.,* 220 mM.

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-M-CSF antibody present at a concentration of 80 to 120 mg/mL, *e.g.,* 100 mg/mL; a buffering agent that comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM); and a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, *e.g.,* 220 mM, at a pH of 5 to 6 (*e.g.*, 5.5).

In some embodiments, the formulation (*e.g.*, liquid formulation) further comprises a surfactant. In certain embodiments, the surfactant is polysorbate 20. In some embodiments, the surfactant or polysorbate 20) is present at a concentration of 0.005 % to 0.1% (w/w), *e.g.,* 0.01% to 0.08%, 0.02% to 0.06%, 0.03% to 0.05%, 0.01% to 0.06%, 0.01% to 0.05%, 0.01% to 0.03%, 0.06% to 0.08%, 0.04% to 0.08%, or 0.02% to 0.08% (w/w), *e.g.*, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, or 0.1% (w/w). In some embodiments, the formulation comprises a surfactant or polysorbate 20 present at a concentration of 0.03% to 0.05%, *e.g.*, 0.04% (w/w).

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-M-CSF antibody present at a concentration of 80 to 120 mg/mL, *e.g.*, 100 mg/mL; a buffering agent that comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM); a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, *e.g.*, 220 mM; and a surfactant or polysorbate 20 present at a concentration of 0.03% to 0.05%, *e.g.,* 0.04% (w/w), at a pH of 5 to 6 (*e.g.*, 5.5).

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-M-CSF antibody present at a concentration of 100 mg/mL; a buffering agent that comprises a histidine buffer (*e.g.*, histidine/histidine-HCL) at a concentration of 20 mM); a carbohydrate or sucrose present at a concentration of 220 mM; and a surfactant or polysorbate 20 present at a concentration of 0.04% (w/w), at a pH of 5 to 6 (*e.g.*, 5.5).

A formulation described herein can be stored in a container. The container used for any of the formulations described herein can include, *e.g.,* a vial, and optionally, a stopper, a cap, or both. In certain embodiments, the vial is a glass vial, *e.g.,* a 6R white glass vial. In other embodiments, the stopper is a rubber stopper, *e.g.,* a grey rubber stopper. In other embodiments, the cap is a flip-off cap, *e.g.,* an aluminum flip-off cap. In some embodiments, the container comprises a 6R white glass vial, a grey rubber stopper, and an aluminum flip-off cap. In some embodiments, the container (*e.g.,* vial) is for a single-use container. In certain embodiments, 25 mg/mL to 250 mg/mL, *e.g.,* 50 mg/mL to 200 mg/mL, 60 mg/mL to 180 mg/mL, 70 mg/mL to 150 mg/mL, 80 mg/mL to 120 mg/mL, 90 mg/mL to 110 mg/mL, 50 mg/mL to 150 mg/mL, 50 mg/mL to 100 mg/mL, 150 mg/mL to 200 mg/mL, or 100 mg/mL to 200 mg/mL, *e.g.,* 50 mg/mL, 60 mg/mL, 70 mg/mL, 80 mg/mL, 90 mg/mL, 100 mg/mL, 110 mg/mL, 120 mg/mL, 130 mg/mL, 140 mg/mL, or 150 mg/mL, of the anti-M-CSF antibody is present in the container (*e.g.,* vial).

In another aspect, the disclosure features therapeutic kits that include the anti-M-CSF antibodies, compositions, or formulations described herein, and instructions for use, *e.g.*, in accordance with dosage regimens described herein.

In a specific embodiment of the invention the anti-M-CSF antibody solution for infusion is formulated as a sterile solution intended for intravenous (IV) administration with the following excipients: sodium chloride, polysorbate 80, and water for Injection. Hydrochloric acid or a combination of L-histidine and L-histidine hydrochloride may be used to adjust the pH.

Administration Methods and Rates

The antibodies disclosed herein can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred route/mode of administration is intravenous injection or infusion. See for example, Sachs et al., Optimal Dosing for Targeted Therapies in Oncology: Drug Development Cases Leading by Example, Clin. Cancer Res; 22(6) 2016; Bai et al, A Guide to Rational Dosing of Monoclonal Antibodies, Clin. Pharmacokinet. 2012: 51 (2) 119-135.

For example, the antibody can be administered by intravenous infusion at a rate of more than 20 mg/min, *e.g.*, 20-40 mg/min, and typically greater than or equal to 40 mg/min to reach a dose of about 35 to 440 mg/m^2, typically about 70 to 310 mg/m^2, and more typically, about 110 to 130 mg/m^2. In embodiments, the antibody can be administered by intravenous infusion at a rate of less than 10mg/min; preferably less than or equal to 5 mg/min to reach a dose of about 1 to 100 mg/m ^{2}, preferably about 5 to 50 mg/m^2, about 7 to 25 mg/m^2 and more preferably, about 10 mg/m^2 . The route and/or mode of administration will vary depending upon the desired results.

Timing

The dosing schedule can vary from e.g., once a week to once every 2, 3, 4, 5, or 6 weeks. In a specific embodiment of the invention the agents used in the dosing regime (e.g. anti-M-CSF antibody and at least one or more of anti-PD-1 antibody, gemcitabine or nab-paclitaxel) are administered once every two weeks. In another specific embodiment of the invention the agents used in the dosing regime (e.g. anti-M-CSF antibody and at least one or more of anti-PD-1 antibody, gemcitabine or nab-paclitaxel) are administered once every three weeks. In yet another specific embodiment the agents used in the dosing regime (e.g anti-M-CSF antibody and at least one or more of anti-PD-1 antibody, gemcitabine or nab-paclitaxel) are administered once every four weeks.

Weight Dosage

An antibody can be dosed according to the weight of the patient. In an embodiment of the invention the weight of the patient is calculated from the individual subjects' body weight as measured at the screening visit and subsequent visits prior to the administration.

In certain embodiments, the anti-PD-1 antibody is administered by injection (*e.g.*, subcutaneously or intravenously) at a dose of about 1 to about 15 mg/kg, about 3 to about 15 mg/kg, about 3 to about 10 mg/kg, or about 6 mg/kg.

In another specific embodiment of the invention the anti-M-CSF antibody is administered by injection (*e.g.*, subcutaneously or intravenously) at a dose of about 1 to 20 mg/kg, of about 1 to 15 mg/kg, *e.g.*, 1 to 10 mg/kg, *e.g.*, about 1 mg/kg, about 3 mg/kg, about 5 mg/kg, about 7.5 mg/kg or about 10 mg/kg.

In one embodiment the anti-M-CSF antibody is administered intravenously at a dose of about 7.5 mg/kg. In more specific embodiment the anti-M-CSF antibody is administered intravenously at a dose of about 7.5 mg/kg once every three weeks. In an alternative specific embodiment the anti-M-CSF antibody is administered intravenously at a dose of about 7.5 mg/kg once every four weeks. In another embodiment the anti-M-CSF antibody is administered intravenously at a dose of about 10 mg/kg. In another more specific embodiment the anti-M-CSF antibody is administered intravenously at a dose of about 10 mg/kg once every four weeks.

In another embodiment the anti-M-CSF antibody is administered intravenously at a dose of about 5 mg/kg. In another more specific embodiment the anti-M-CSF antibody is administered intravenously at a dose of about 5 mg/kg once every two weeks.

In a specific embodiment the anti-M-CSF antibody, for example MCS110, is administered intravenously at a dose of about 1 mg/kg every three weeks and the PD-1 inhibitor, for example PDR001, is administered intravenously at a dose of about 300 mg every three weeks to treat pancreatic cancer.

Flat Dosage

Antibodies can also be administered to patients as a flat dosage, that is giving a fixed or predetermined amount of dosage to each patient. The terms flat dosage and fixed dosage are used interchangeably. Flat or fixed dosing can be beneficial to patients, for example, to save drug supply and to reduce pharmacy errors.

In some embodiments, the anti-PD-1 antibody is administered by injection (*e.g.*, subcutaneously or intravenously) at a dose (*e.g.,* a flat dose) of about 100 mg to 500 mg, *e.g.,* about 250 mg to 450 mg, about 300 mg to 400 mg, about 250 mg to 350 mg, about 350 mg to 450 mg, or about 300 mg or about 400 mg. In one embodiment, the anti-PD-1

antibody is administered at a dose from about 300 mg to 400 mg once every three weeks or once every four weeks. In one embodiment, the anti-PD-1 antibody is administered at a dose about 300 mg once every three weeks. In one embodiment, the anti-PD-1 antibody is administered at a dose from about 400 mg once every four weeks. In one embodiment, the anti-PD-1 antibody is administered at a dose from about 300 mg once every four weeks. In one embodiment, the anti-PD-1 antibody is administered at a dose from about 400 mg once every three weeks.

The anti-M-CSF antibody can likewise be administered as a flat dosage. In some embodiments, the anti-M-CSF antibody is administered by injection (*e.g.*, subcutaneously or intravenously) at a dose (*e.g.,* a flat dose) of about 50 mg to 1200 mg, *e.g.,* about 100 mg to 1050 mg, about 100 mg to 1000 mg. In one embodiment, the anti-M-CSF antibody is administered at a dose from about 300 mg to 1000 mg once every four weeks. In another embodiment, the anti-M-CSF antibody is administered at a dose from about 100 mg to about 600 mg once every two weeks.

A flat dose may also be matched to a predefined body weight range, such that a specific flat dose is given to a patient within a certain body weight range.

Therapeutic Use

In one aspect, a method of treating (*e.g.*, one or more of reducing, inhibiting, or delaying progression) a cancer or a tumour in a subject is provided. The method comprises administering to the subject an anti-M-CSF antibody described herein in accordance with a dosage regimen described herein, alone or in combination with one or more therapeutic agents, procedures, or modalities.

In an embodiment of the invention, the cancer is a solid tumour. In a specific embodiment of the invention, the cancer is selected from the group consisting of pancreatic cancer, melanoma, breast cancer and endometrial cancer. In another specific embodiment, the breast cancer is triple negative breast cancer (TNBC). In yet another specific embodiment, the melanoma has been previously resistant to PD-1/PD-L1 directed therapy. In a further specific embodiment the cancer is endometrial cancer. In one preferred embodiment, the cancer is pancreatic cancer. In another preferred embodiment, the pancreatic cancer is pancreatic adenocarcinoma. In yet another preferred embodiment the pancreatic cancer is metastatic pancreatic ductal adenocarcinoma. In a specific embodiment, the antibody or antigen binding fragment for

use or method of treating cancer is for use in a method of first line (1L) therapy to treat metastatic pancreatic ductal adenocarcinoma.

Tumour response may be determined locally according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (Therasse et al., (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumours, Journal of National Cancer Institute, Vol. 92; 205-16); New Guidelines to Evaluate the Response in Solid Tumours, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

In one example, the dosage regime described herein can be used for the treatment of pancreatic cancer. Cancer subjects receiving the dosage regime can be patients with pancreatic cancer who have been previously treated with standard of care or patients who have not yet received any treatment. In one example, the dosage regime described herein is used to treat patients having advanced pancreatic cancer who have been treated with standard of care or who are receiving the standard of care but show disease progression.

Thus the dosage regime of an embodiment of the invention provides a method of inhibiting growth of tumour cells in a subject, comprising administering to the subject a therapeutically effective amount of the agents (e.g anti-M-CSF antibody and at least one or more of anti-PD-1 antibody, gemcitabine or nab-paclitaxel) described herein. In another embodiment, the dosage regimes described herein can be administered alone or in combination with one or more other agents, and the combination can be administered in either order or simultaneously. In one example, the dosage regimes disclosed herein can be co-administered with one or more additional therapeutic agents, *e.g.*, one or more anti-cancer agents, cytotoxic or cytostatic agents, hormone treatment, vaccines, and/or other immunotherapies. In other embodiments, the dosage regimes disclosed herein can be administered in combination with other therapeutic treatment modalities, including surgery, radiation, cryosurgery, and/or thermotherapy.

EXAMPLES

The Examples below are set forth to aid in the understanding of the inventions but are not intended to, and should not be construed to, limit its scope in any way.

Example 1

A Phase Ib/II clinical trial is performed in adult patients with solid tumours (advanced melanoma, endometrial carcinoma, pancreatic adenocarcinoma or triple negative breast cancer (TNBC)). The purpose of this study of MCS110 with PDR001 is to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of the combination of MCS110 with PDR001 in adult patients with solid tumors. MCS110 and PDR001 are administered once every 3 weeks via i.v. infusions over 30 minutes and 1 hour, respectively. The drugs are administered separately with at least a 30 min break between the two antibodies. Infusions of each antibody can be extended to up to 2 hours if clinically indicated. The dosing regime is used as set out in Table 6 and Table 7.

Starting dose

The starting dose and regimen of MCS110 will be 3 mg/kg iv every 3 weeks, corresponding to approximately 40 % of the single agent dose administered in PVNS patients (10 mg/kg every 4 weeks in study NCT01643850, CMCS110X2201)) and 30 % of the dose administered in combination with carboplatin/gemcitabine in TNBC (10 mg/kg every 3 weeks in study NCT02435680, CMCSZ2201).

The starting dose and regimen of PDR001 is 100 mg iv every 3 weeks. PDR001 has been tested up to the dose of 10 mg/kg every 2 weeks in the NCT02404441, CPRD001X2101 study. The PDR001 exposure at a starting dose of 100 mg Q3W is within the range of those observed in the CPDR001X2101 study with no DLTs. PDR001 is expected to demonstrate anti-tumour activity at doses of 100 mg or above every 3 weeks.

Table 6 Dosing regimen MCS110 and PDR001

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
MCS110	Liquid concentrate in vial i.v. infusion	3 mg/kg (starting dose)	Every 3 weeks
PDR001	Lyophilisate in vial i.v. infusion	100 mg (starting dose)	Every 3 weeks

Table 7

dose MCS110	dose PDR001
1 mg/kg Q3W	100 mg Q3W
1 mg/kg Q3W	300 mg Q3W
3 mg/kg Q3W	100 mg Q3W
3 mg/kg Q3W	300 mg Q3W
5 mg/kg Q3W	300 mg Q3W
7.5 mg/kg Q3W	300 mg Q3W
10 mg/kg Q3W	300 mg Q3W

Both study drugs may be infused using the same i.v. access site. The same administration sequence is followed for all patients, i.e. PDR001 should be infused first. If an infusion reaction occurs after administration of PDR001, the subsequent MCS110 infusion is delayed until it is safe for the patient to receive MCS110 based on the clinical discretion of the investigator. The delay between PDR001 and MCS110 infusions can be up to 4 hours if clinically indicated.

A scheduled dose of ongoing study drugs may be delayed by up to 7 days to recover from previous AEs or a missed visit. If a scheduled dose of ongoing study drugs is delayed longer than 7 days due to an unresolved AE, the administration should be skipped and treatment resumed at a lower dose level (if meeting criteria for DLT) at the next scheduled dose. The assessment schedule will be shifted accordingly. Dose delays refer to all ongoing study drugs: for combination treatment both MCS110 and PDR001 and for single agent treatment MCS110 or PDR001. The dose for MCS110 study drug is calculated from the individual subjects' body weight as measured at the screening visit and subsequent visits prior to the administration.

Primary outcome measures

1. (phase 1) Number of patients with adverse events, as a measure of safety [Time Frame: two cycles of treatment; cycle = 21 days]
2. (phase 2) : Overall Response rate (ORR) [Time Frame: 6 months of treatment]

Secondary outcome measures

1. Phase 1: Overall Response Rate (ORR) [Time Frame: 6 months of treatment]
2. Phase 1: progression free survival (PFS) [Time Frame: 6 months of treatment]
3. Phase 2 Overall response rate per immune related Response Criteria [Time Frame: 6 months of treatment]
4. Phase 1 : clinical benefit rate (CBR) [Time Frame: 6 months of treatment]
5. Phase 1 : duration of response (DOR) [Time Frame: 6 months of treatment]
6. Phase 1 : disease control rate (DCR) [Time Frame: 6 months of treatment]
7. Phase 2 : Progression Free Survival (PFS) [Time Frame: 6 months of treatment]
8. Phase 2 Duration Of Response (DOR) [Time Frame: 6 months of treatment]
9. Phase 2 : Disease Control Rate (DCR) [Time Frame: 6 months of treatment]
10. Phase 2 : Clinical Benefit Rate (CBR) [Time Frame: 6 months of treatment]

Example 2

As of April 10, 2018, 60 patients received lacnotuzumab + spartalizumab at escalating doses as above. The combination of lacnotuzumab + spartalizumab demonstrated a tolerable safety profile in patients with advanced malignancies. Partial response according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 was achieved by 2 patients. One in the lacnotuzumab 1 mg/kg + spartalizumab 100 mg dose level and 1 in the lacnotuzumab 10 mg/kg + spartalizumab 300 mg dose level. Both patients were diagnosed with pancreatic cancer. Stable disease according to RECIST v1.1 was achieved by 11 (18.3%) patients (**Table 8**).

In evaluable patients with pancreatic cancer (n=26), the best overall responses were partial response (n=2), stable disease (n=4), and progressive disease (n=20).

Table 8. Best Overall Response as per Investigator Based on RECIST v1.1 by Treatment

Response	**lacnotuzumab 1 mg/kg + spartalizumab 100mg (n=6)**	**lacnotuzumab 3 mg/kg + spartalizumab 100mg (n=12)**	**lacnotuzumab 3 mg/kg + spartalizumab 300mg (n=12)**
BOR, n (%)			
PR	1 (16.7)	0	0
SD	1(16.7)	5 (41.7)	0
PD	4(66.7)	6(50.0)	9(75.0)
unknown	0	1(8.3)	3(25.0)
DCR, n(%)	2 (33.3)	5(41.7)	0
[90% CI]	[6.3-72.9]	[18.1-68.5]	[0-22.1]
Response	**lacnotuzumab 5mg/kg + spartalizumab 300mg (n=13)**	**lacnotuzumab 7.5 mg/kg + spartalizumab 300mg (n=6)**	**lacnotuzumab 10mg/kg + spartalizumab 300mg (n=11)**
BOR, n (%)			
PR	0	0	1(9.1)
SD	2(15.4)	1(16.7)	2(18.2)
PD	7(53.8)	4(66.7)	4(36.4)
unknown	4(30.8)	1(16.7)	4(36.4)
DCR, n(%)	2(15.4)	1(16.7)	3(27.3)
[90% CI]	[2.8-41.0]	[0.9-58.2]	[7.9-56.4]
Response	**All patients (N=60)**		
BOR, n (%)			
PR	2(3.3)		
SD	11(18.3)		
PD	34(56.7)		
unknown	13(21.7)		
DCR, n(%)	13(21.7)		
[90% CI]	[13.3-32.2]		

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BOR, best overall response; CI, confidence interval; DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease;

The RP2D is 7.5 mg/kg Q3W lacnotuzumab and 300 mg Q3W spartalizumab.

Example 3

A ligand binding model was developed to establish the relationship between anti-M-CSF antibody dose and target engagement (CSF-1) in circulation and to support the selection of the RP2D. Total CSF-1 levels in the blood (Total CSF-1: free CSF-1 + complex CSF-1 with MCS110) were measured as the PD marker and used to model the target engagement in circulation. In brief, both free anti-M-CSF antibody and total CSF-1 kinetics data collected from MCS110 study trials were simultaneously fitted using a TMDD model to characterize the dose-target engagement relationship. Model-based simulations were used to determine the anti-M-CSF antibody dose leading to a substantial depletion of circulating free CSF-1 in cancer patients. The pharmacological criterion chosen to guide the dose selection was the ability to achieve at least 90% depletion from baseline of the free circulating CSF-1 in at least 90% of cancer patients. Model-based simulations were used to compute the proportion of cancer patients having a substantial (≥90%) depletion from baseline of circulating free CSF-1 at end of cycle 2. Simulations suggested that doses ≥ 7.5 mg/kg Q3W achieve a substantial (≥90%) depletion from baseline of circulating free CSF-1 in at least 90% of cancer patients at end of cycle 2.

Moreover, model-based simulations were used to determine the anti-M-CSF antibody dose leading to at least 90% depletion from baseline of the free circulating CSF-1 in at least 90% of cancer patients for Q2W and Q4W regimen. Simulation suggested that an anti-M-CSF antibody dose of 5 mg/kg Q2W and 10 mg/kg Q4W would be required for substantial depletion of target.

A model characterizing the relationship between anti-M-CSF antibody dose and CK kinetics was developed to define the therapeutic window for dose selection which mitigates CK elevation while providing substantial target depletion.

Example 4

A clinical trial is performed in adult patients with metastatic pancreatic adenocarcinoma.

Cohort 1: MCS110+ PDR001 + Gemcitabine + Nab-Paclitaxel

MCS110 is administered at 10mg/kg IV infusion once every 28 days.

A lower dose level of MCS110 at 7.5mg/kg is administered if the starting dose is not tolerated.

PDR001 is administered as a 400 mg IV infusion once every 28 days.

Gemcitabine is administered as 1000 mg/m^2 IV on day 1, 8 and 15 of a 28-day cycle.

Nab-Paclitaxel is administered as 125 mg/m^2 IV on day 1, 8 and 15 of a 28-day cycle.

Cohort 2: MCS110 + Gemcitabine + Nab-Paclitaxel

MCS110 is administered at 10 mg/kg IV infusion once every 28 days.

A lower dose level of MCS110 at 7.5mg/kg is administered if the starting dose is not tolerated.

Gemcitabine is administered as 1000 mg/m^2 IV on day 1, 8 and 15 of a 28-day cycle.

Nab-Paclitaxel is administered as 125 mg/m^2 IV on day 1, 8 and 15 of a 28-day cycle.

Example 5

A unified model to predict free CSF1 (efficacy surrogate) and CK (pharmacology related safety endpoint) levels was developed to support the identification of a dosing regimen which would provide the highest proportion of patients within an acceptable therapeutic window based on pre-defined boundaries for efficacy (for example, ≥90% free CSF1 depletion in circulation at end of dosing interval) and safety (for example < 20% of subjects experiencing a grade 4 CK elevation). Preliminary model-based simulation using the aforementioned criteria, identified the dose regimen of 5 mg/kg Q2W to provide acceptable benefit/risk ratio by maximizing CSF-1 target engagement throughout the dosing interval, while limiting the incidences of CK elevation.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

What is claimed is:

1. An isolated antibody or antigen binding fragment capable of binding to macrophage colony stimulating factor 1 (M-CSF) for use at dose of about 5 mg/kg once every two weeks, or at a dose of 7.5 mg /kg once every three weeks or at a dose of about 7.5 mg /kg once every four weeks or at a dose of about 10 mg /kg once every four weeks in treating a cancer in a subject, wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

2. A method of treating a cancer in a subject, the method comprising administering to the subject an isolated antibody or antigen binding fragment capable of binding to macrophage colony stimulating factor 1 (M-CSF) at a dose of about 5 mg/kg once every two weeks, or at a dose of about 7.5 mg /kg once every three weeks or at a dose of about 7.5 mg /kg once every four weeks or at a dose of about 10 mg /kg once every four weeks, wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

3. The antibody or antigen binding fragment for use of claim 1, or the method of claim 2, wherein the cancer is selected from the group consisting of pancreatic cancer, melanoma, breast cancer and endometrial cancer.

4. The antibody or antigen binding fragment for use of claim 1 or 3, or the method of claim 2 or 3, wherein the cancer is metastatic pancreatic ductal adenocarcinoma.

5. The antibody or antigen binding fragment for use according to any one of claims 1 or 3 or 4, or the method of any one of claims 2 to 4, wherein the antibody or antigen binding fragment capable of binding to M-CSF is used in combination with a PD-1 inhibitor selected from the group consisting of spartalizumab, nivolumab, pembrolizumab,

pidilizumab, MEDI0680, REGN2810, PF-06801591, BGB-A317, BGB-108, INCHR1210, TSR-042, and AMP-224.

6. The antibody or antigen binding fragment for use according to claim 5, or the method according to claim 5, wherein the PD-1 inhibitor is spartalizumab.

7. The antibody or antigen binding fragment for use according to claims 5 or 6, or the method according to claim 5 or 6, wherein the PD-1 inhibitor is used at a dose of about 300 mg once every three weeks or about 400 mg once every four weeks.

8. The antibody or antigen binding fragment for use according to any one of claims 5 to 7, or the method according to any one of claims 5 to 7, wherein the antibody or antigen binding fragment capable of binding to M-CSF is used at a dose of about 7.5 mg/kg once every three weeks and the PD-1 inhibitor is used at a dose of about 300 mg once every three weeks or the antibody or antigen binding fragment capable of binding to M-CSF is used at a dose of about 7.5 mg /kg once every four weeks and the PD-1 inhibitor is used at a dose of about 400 mg once every four weeks or the antibody or antigen binding fragment capable of binding to M-CSF is used at a dose of about 10 mg /kg once every four weeks and the PD-1 inhibitor is used at a dose of about 400 mg once every four weeks.

9. The antibody or antigen binding fragment for use according to any one of claims 5 to 7, or the method according to any one of claims 5 to 7, wherein the antibody or antigen binding fragment capable of binding to M-CSF is used at a dose of about 5 mg/kg once every two weeks and the PD-1 inhibitor is used at a dose of about 300 mg once every three weeks or the antibody or antigen binding fragment capable of binding to M-CSF is used at a dose of about 5 mg /kg once every two weeks and the PD-1 inhibitor is used at a dose of about 400 mg once every four weeks.

10. The antibody or antigen binding fragment for use of any one of claims 1 or 3 to 9, or the method of any one of claims 2 to 9, wherein the antibody or antigen binding fragment capable of binding to M-CSF is used in combination with gemcitabine.

11. The antibody or antigen binding fragment for use according to claim 10, or the method according to claim 10, wherein the gemcitabine is administered as 1000 mg/m^2 three times within four weeks.

12. The antibody or antigen binding fragment for use of any one of claims 1 or 3 to 11, or the method of any one of claims 2 to 11, wherein the antibody or antigen binding fragment capable of binding to M-CSF is used in combination with nab-paclitaxel.

13. The antibody or antigen binding fragment for use according to claim 12, or the method according to claim 12, wherein the nab-paclitaxel is administered as 125 mg/m^2 three times within four weeks.

14. A pharmaceutical composition or dose formulation comprising an antibody or antigen binding fragment capable of binding to M-CSF for use at a dose of about 7.5 mg /kg once every three weeks or at a dose of about 7.5 mg /kg once every four weeks or at a dose of about 10 mg /kg once every four weeks, in treating a cancer in a subject, wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

15. A pharmaceutical composition or dose formulation comprising an antibody or antigen binding fragment capable of binding to M-CSF for use at a dose of about 5 mg /kg once every two weeks, in treating a cancer in a subject, wherein the antibody or antigen binding fragment comprises (a) VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 6, a VHCDR2 amino acid sequence of SEQ ID NO: 7 and a VHCDR3 amino acid sequence of SEQ ID NO:8; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 9, a VLCDR2 amino acid sequence of SEQ ID NO:10 and a VLCDR3 amino acid sequence of SEQ ID NO: 11.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/057235

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 A61P35/00 C07K16/24 C07K16/28
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2017/017623 A1 (NOVARTIS AG [CH]; FJAELLSKOG MARIE-LOUISE [US] ET AL.) 2 February 2017 (2017-02-02) page 2, line 15 - line 22 page 16 - page 18; table 1 page 22 - page 24; table 2 page 43, line 22 - page 46, line 27 example 1 table 6 ----- -/--	1-15

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
9 December 2019	13/01/2020

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2019/057235

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