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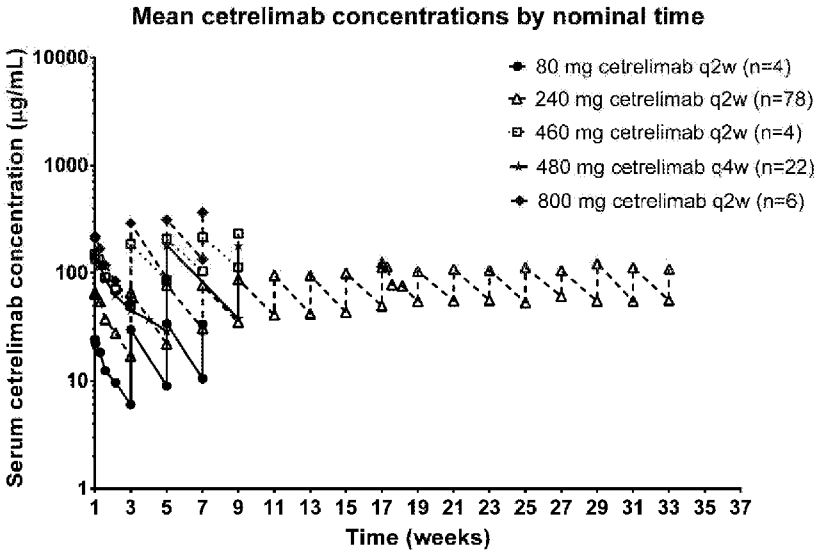
(54) Title: METHODS OF TREATING CANCERS WITH ANTAGONISTIC ANTI-PD-1 ANTIBODIES

FIG. 1



(57) Abstract: The present invention relates to methods of treating cancers with antagonistic anti-PD-1 antibodies, formulations of the antagonistic anti-PD-1 antibodies and drug products of the anti- PD-1 antibodies.

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[Continued on next page]

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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METHODS OF TREATING CANCERS WITH ANTAGONISTIC ANTI-PD-1 ANTIBODIES

FIELD OF THE INVENTION

The present invention relates to methods of treating cancers with antagonistic anti-PD-1 antibodies, formulations of the antagonistic anti-PD-1 antibodies and drug products of the anti-PD-1 antibodies.

SEQUENCE LISTING

This application contains a Sequence Listing submitted via EFS-Web, the entire content of which is incorporated herein by reference. The ASCII text file, created on 18 January 2019, is named JBI5152WOPCT1_ST25.txt and is 12 kilobytes in size.

BACKGROUND OF THE INVENTION

The immune system is tightly controlled by a network of costimulatory and co-inhibitory ligands and receptors. These molecules provide secondary signals for T cell activation and provide a balanced network of positive and negative signals to maximize immune responses against infection and tumors, while limiting immunity to self (Wang *et al.,* (Epub Mar. 7, 2011) *J Exp Med* 208(3):577-92; Lepenies *et al.*, (2008) *Endocr Metab Immune Disord Drug Targets* 8:279-288). Immune checkpoint therapy, targeting co-inhibitory pathways in T cells to promote antitumor immune responses, has led to advances in clinical care of cancer patients.

PD-1 is a negative immune checkpoint molecule that suppresses $CD4^+$ and $CD8^+$ T cell functions in the tumor microenvironment (TME). PD-1 engagement with its ligands (PD-L1 and PD-L2) drives T cell anergy and exhaustion in tumors by inhibiting multiple pathways downstream of the T cell receptor signaling, resulting in decreased T cell survival, growth and proliferation, compromised effector function, and altered metabolism. Preclinical studies have demonstrated that the PD-1 pathway blockade can reverse T cell exhaustion and stimulate anti-tumor immunity.

While anti-PD-1/PD-L1 antibodies are demonstrating encouraging clinical responses in patients with multiple solid tumors, the response rates are still fairly low, about 15% - 20% in pretreated patients (Swaika *et al., (*2015) *Mol Immunol.* doi: 10.1016/j.molimm.2015.02.009).

Therefore, there is a need for new therapeutics that inhibit the immunosuppressive activity of checkpoint inhibitors such as PD-1 to be used for cancer immunotherapy.

SUMMAY OF THE INVENTION

The invention provides a method of treating a cancer, comprising administering to a subject diagnosed with the cancer an antagonistic anti-PD1 antibody or an antigen binding fragment thereof, comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 at a dose of between about 240 mg and about 480 mg.

The invention also provides a pharmaceutical composition comprising
between about 10 mg/ml and about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
about 10 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
a lyophilized formulation comprising between about 90 mg and about 240 mg of cetrelimab and one or more pharmaceutically acceptable excipients;
a lyophilized formulation comprising about 90 mg of cetrelimab and one or more pharmaceutically acceptable excipients; or
a lyophilized formulation comprising about 240 mg of cetrelimab and one or more pharmaceutically acceptable excipients.

The invention also provides a drug product comprising
between about 10 mg/ml and about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
about 10 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
a lyophilized formulation comprising between about 90 mg and about 240 mg of cetrelimab and one or more pharmaceutically acceptable excipients;
a lyophilized formulation comprising about 90 mg of cetrelimab and one or more pharmaceutically acceptable excipients; or
a lyophilized formulation comprising about 240 mg of cetrelimab and one or more pharmaceutically acceptable excipients.

The invention also provides a drug product comprising

between about 10 mg/ml and about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
about 10 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
a lyophilized formulation comprising between about 90 mg and about 240 mg of cetrelimab and one or more pharmaceutically acceptable excipients;
a lyophilized formulation comprising about 90 mg of cetrelimab and one or more pharmaceutically acceptable excipients; or
a lyophilized formulation comprising about 240 mg of cetrelimab and one or more pharmaceutically acceptable excipients,
for the treatment of a cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the mean serum concentration (µg/ml) of JNJ-63723283 (cetrelimab) over time in subjects dosed 80 mg, 240 mg, 460 mg, 480 mg or 800 mg once in two weeks (q2w) or once in four weeks (q4w) as indicated. The number of patients (n) dosed is shown in parenthesis.

FIG. 2 shows the percentage (%) of PD-1 receptor occupancy of JNJ-63723283 (cetrelimab) on $CD3^+$ circulating T cells over time (as indicated by administered doses 1-39) in subjects dosed 240 mg cetrelimab q2w. Pre: before dosing; EOI+2H: End of infusion plus 2 hours. EOI+1H: end of infusion plus 1 hour. EOT: end of treatment.

FIG. 3 shows the percentage (%) of PD-1 receptor occupancy of JNJ-63723283 (cetrelimab) on $CD3^+$ circulating T cells over time (as indicated by administered doses 1-14) in subjects dosed 480 mg cetrelimab q4w. Pre: before dosing; EOI+2H: End of infusion plus 2 hours. EOI+1H: end of infusion plus 1 hour. EOT: end of treatment.

FIG. 4 shows the time course of T cell activation in patient receiving 240 mg once every two weeks (Q2W) (solid line) or 480 mg once every four weeks (Q4W) (dashed line) JNJ-63723283 (cetrelimab). Ratio of 1 indicates maximum T cell activation. D = dose; EOT = end of treatment (time points vary per patient); FU = follow-up; Pre = pre-infusion; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SEB = staphylococcal enterotoxin B.

DETAILED DESCRIPTION OF THE INVENTION

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

It is to be understood that the terminology used herein is for the purpose of describing embodiments only and is not intended to be limiting. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains.

Although any methods and materials similar or equivalent to those described herein may be used in the practice for testing of the present invention, exemplary materials and methods are described herein. In describing and claiming the present invention, the following terminology will be used.

As used in this specification and the appended claims, the singular forms "a," "an," and "**the**" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a cell" includes a combination of two or more cells, and the like.

The transitional terms "**comprising**," "**consisting essentially of**," and "**consisting of**" are intended to connote their generally accepted meanings in the patent vernacular; that is, (i) "comprising," which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; (ii) "consisting of" excludes any element, step, or ingredient not specified in the claim; and (iii) "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. Embodiments described in terms of the phrase "comprising" (or its equivalents) also provide as embodiments those independently described in terms of "consisting of" and "consisting essentially of."

"**Antagonist**" or "**antagonistic**" refers to an anti-PD1 antibody which upon binding to PD-1 suppresses at least one biological activity mediated by PD-1 ligand PD-L1 or PD-L2. The anti-PD-1 antibody is an antagonist when the at least one biological activity mediated by PD-L1 or PD-L2 is suppressed by at least about 20%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% greater than in the absence of the antagonist (*e.g.*, negative control), or when the suppression is statistically significant when compared to the suppression in the absence of the antagonist. A typical biological activity that is mediated by PD-L1 or PD-L2 binding to PD-1 is inhibition of antigen-specific $CD4^+$ and/or $CD8^+$ T cells. Therefore, antagonistic antibody relieves PD-L1 mediated suppression resulting in enhancement of immune responses.

"**PD-1**" refers to human programmed cell death protein 1, PD-1. PD-1 is also known as CD279 or PDCD1. The amino acid sequence of the mature human PD-1 (without signal sequence) is shown in **SEQ ID NO: 11**. The extracellular domain spans residues 1-150, the transmembrane domain spans residues 151-171 and the cytoplasmic domain spans residues 172-268 of **SEQ ID NO: 11.**

SEQ ID NO: 11

PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLA
AFPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLR
AELRVTERRAEVPTAHPSPSPRPAGQFQTLVVGVVGGLLGSLVLLVWVLAVICSRAARG
TIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQTEYATIVFPSGMG
TSSPARRGSADGPRSAQPLRPEDGHCSWPL

"**Antibodies**" is meant in a broad sense and includes immunoglobulin molecules belonging to any class, IgA, IgD, IgE, IgG and IgM, or sub-class IgA1, IgA2, IgG1, IgG2, IgG3 and IgG4 and including either kappa (κ) and lambda (λ) light chain. Antibodies include monoclonal antibodies, full length antibodies, antigen binding fragments, bispecific or multispecific antibodies, dimeric, tetrameric or multimeric antibodies, single chain antibodies, domain antibodies and any other modified configuration of the immunoglobulin molecule that comprises an antigen binding fragment of the required specificity. "**Full length antibodies**" are comprised of two heavy chains (HC) and two light chains (LC) inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region (comprised of domains CH1, hinge, CH2 and CH3). Each light chain is comprised of a light chain variable region (VL) and a light chain constant region (CL). The VH and the VL may be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with framework regions (FR). Each VH and VL is composed of three CDRs and four FR segments, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. Antibodies include antibodies generated using various technologies, including antibodies generated from immunized mice or rat or identified from phage or mammalian display libraries as described herein.

"**Complementarity determining regions (CDR)**" are antibody regions that bind an antigen. There are three CDRs in the VH (HCDR1, HCDR2, HCDR3) and three CDRs in the VL (LCDR1, LCDR2, LCDR3). CDRs may be defined using various delineations such as Kabat

(Wu et al. (1970) *J Exp Med* 132: 211-50) (Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991), Chothia (Chothia *et al.* (1987) *J Mol Biol* 196: 901-17), IMGT (Lefranc *et al.* (2003) *Dev Comp Immunol* 27: 55-77) and AbM (Martin and Thornton (1996) *J Bmol Biol* 263: 800-15). The correspondence between the various delineations and variable region numbering are described (see e.g. Lefranc *et al.* (2003) *Dev Comp Immunol* 27: 55-77; Honegger and Pluckthun, (2001) *J Mol Biol* 309:657-70; International ImMunoGeneTics (IMGT) database; Web resources, http://www_imgt_org). Available programs such as abYsis by UCL Business PLC may be used to delineate the CDRs. The term "CDR", "HCDR1", "HCDR2", "HCDR3", "LCDR1", "LCDR2" and "LCDR3" as used herein includes CDRs defined by any of the methods described supra, Kabat, Chothia, IMGT or AbM, unless otherwise explicitly stated in the specification.

"**Antigen binding fragment**" refers to a portion of an immunoglobulin molecule that retains the antigen binding properties of the parental full length antibody. Exemplary antigen binding fragments are heavy chain complementarity determining regions (HCDR) 1, 2 and/or 3, light chain complementarity determining regions (LCDR) 1, 2 and/or 3, the VH, the VL, the VH and the VL, Fab, F(ab')2, Fd and Fv fragments as well as domain antibodies (dAb) consisting of either one VH domain or one VL domain. The VH and the VL domains may be linked together via a synthetic linker to form various types of single chain antibody designs in which the VH/VL domains pair intramolecularly, or intermolecularly in those cases when the VH and VL domains are expressed by separate chains, to form a monovalent antigen binding site, such as single chain Fv (scFv) or diabody; described for example in Int. Pat. Publ. No. WO1998/44001, Int. Pat. Publ. No. WO1988/01649; Int. Pat. Publ. No. WO1994/13804; Int. Pat. Publ. No. WO1992/01047.

"**Humanized antibody**" refers to an antibody in which CDR sequences are derived from non-human species and the frameworks are derived from human immunoglobulin sequences. Humanized antibody may include substitutions in the framework so that the framework may not be an exact copy of expressed human immunoglobulin or human immunoglobulin germline gene sequences. Antibodies in which at least one CDR is derived from non-human species and at least one framework is derived from human immunoglobulin sequences are humanized antibodies. Humanized antibody may include substitutions in the frameworks so that the frameworks may not be exact copies of expressed human immunoglobulin or human immunoglobulin germline gene sequences.

"**Human antibody**" refers to an antibody that is optimized to have minimal immune response when administered to a human subject. Variable regions of human antibody are derived from human germline immunoglobulin sequences. If the antibody contains a constant region or a

portion of the constant region, the constant region is also derived from human germline immunoglobulin sequences.

Human antibody comprises heavy or light chain variable regions that are "derived from" human germline immunoglobulin sequences if the variable regions of the antibody are obtained from a system that uses human germline immunoglobulin genes. Such exemplary systems are human immunoglobulin gene libraries displayed on phage or mammalian cells, and transgenic non-human animals such as mice, rats or chicken carrying human immunoglobulin loci. "Human antibody" typically contains amino acid differences when compared to the immunoglobulins expressed in humans due to differences between the systems used to obtain the antibody and human immunoglobulin loci, introduction of naturally occurring somatic mutations, intentional introduction of substitutions into the framework or the CDRs. "Human antibody" is typically about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical in amino acid sequence to an amino acid sequence encoded by human germline immunoglobulin sequences. In some cases, "human antibody" may contain consensus framework sequences derived from human framework sequence analyses, for example as described in (Knappik *et al.* (2000) *J Mol Biol* 296: 57-86), or synthetic HCDR3 incorporated into human immunoglobulin gene libraries displayed on phage, for example as described in (Shi *et al.* (2010) *J Mol Biol* 397: 385-96), and in Int. Patent Publ. No. WO2009/085462. Antibodies in which CDRs are derived from a non-human species are not included in the definition of "human antibody".

"**Monoclonal antibody**" refers to an antibody population with single amino acid composition in each antibody chain except for possible well known alterations such as removal of C-terminal lysine from the antibody heavy chain or alterations due to post-translational modification(s) of amino acids, such as methionine oxidation or asparagine or glutamine deamidation. Monoclonal antibodies typically specifically bind one antigenic epitope, except that bispecific or multispecific monoclonal antibodies specifically bind two or more distinct antigenic epitopes. Monoclonal antibodies may have heterogeneous glycosylation within the antibody population. Monoclonal antibody may be monospecific or multispecific, or monovalent, bivalent or multivalent. A bispecific antibody is included in the term monoclonal antibody.

"**Isolated**" refers to a homogenous population of molecules (such as synthetic polynucleotides or a protein such as an antibody) which have been substantially separated and/or purified away from other components of the system the molecules are produced in, such as a recombinant cell, as well as a protein that has been subjected to at least one purification or isolation step. "Isolated antibody" refers to an antibody that is substantially free of other cellular

material and/or chemicals and encompasses antibodies that are isolated to a higher purity, such as to 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% purity.

A "**cancer cell**" or a "**tumor cell**" refers to a cancerous, pre-cancerous or transformed cell, either *in vivo*, *ex vivo*, or in tissue culture, that has spontaneous or induced phenotypic changes. These changes do not necessarily involve the uptake of new genetic material. Although transformation may arise from infection with a transforming virus and incorporation of new genomic nucleic acid, uptake of exogenous nucleic acid or it can also arise spontaneously or following exposure to a carcinogen, thereby mutating an endogenous gene. Transformation/cancer is exemplified by morphological changes, immortalization of cells, aberrant growth control, foci formation, proliferation, malignancy, modulation of tumor specific marker levels, invasiveness, tumor growth in suitable animal hosts such as nude mice, and the like, *in vitro*, *in vivo*, and *ex vivo* (Freshney, Culture of Animal Cells: A Manual of Basic Technique (3rd ed. 1994)).

"**Cancer**" refers to a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth results in the formation of malignant tumors that invade neighboring tissues and may also metastasize to distant parts of the body through the lymphatic system or bloodstream. A "cancer" or "cancer tissue" can include a tumor.

"**About**" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. Unless explicitly stated otherwise within the Examples or elsewhere in the Specification in the context of a particular assay, result or embodiment, "about" means within one standard deviation per the practice in the art, or a range of up to 5%, whichever is larger.

"**Subject**" includes any human or nonhuman animal. "Nonhuman animal" includes all vertebrates, *e.g.,* mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, chickens, amphibians, reptiles, etc. The terms "subject" and "patient" can be used interchangeably herein.

"**Treat**" or "**treatment**" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as growth and/or spreading of tumor cells. Beneficial or desired clinical results include alleviation of symptoms, shrinkage of tumor size, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease

progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if a subject was not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

"**Therapeutically effective amount**" refers to an amount effective, at doses and for periods of time necessary, to achieve a desired therapeutic result. A therapeutically effective amount may vary depending on factors such as the disease state, age, sex, and weight of the individual, and the ability of a therapeutic or a combination of therapeutics to elicit a desired response in the individual. Exemplary indicators of an effective therapeutic or combination of therapeutics that include, for example, improved well-being of the patient.

"**Anti-PD-1 antibody**" refers to an antibody that specifically binds PD-1.

"**Specifically binds**", "**specific binding**" or "**binds**" refer to antibody binding to an antigen (e.g. PD-1) or an epitope within the antigen with greater affinity than for other antigens. Typically, the antibody binds to the antigen or the epitope within the antigen with an equilibrium dissociation constant (K_D) of about $1x10^{-8}$ M or less, for example about $1x10^{-9}$ M or less, about $1x10^{-10}$ M or less, about $1x10^{-11}$ M or less, or about $1x10^{-12}$ M or less, typically with a K_D that is at least one hundred-fold less than its K_D for binding to a non-specific antigen (e.g., BSA, casein). The K_D may be measured using standard procedures. Antibodies that specifically bind to the antigen or the epitope within the antigen may, however, have cross-reactivity to other related antigens, for example to the same antigen from other species (homologs), such as human or monkey, for example *Macaca fascicularis* (cynomolgus, cyno), *Pan troglodytes* (chimpanzee, chimp) or *Callithrix jacchus* (common marmoset, marmoset).

"**Dosage**" refers to the information of the amount of the therapeutic to be taken by the subject and the frequency of the number of times the therapeutic is to be taken by the subject.

"**Dose**" refers to the amount or quantity of the therapeutic to be taken each time.

"Relapsed" refers to the return of a disease or the signs and symptoms of a disease after a period of improvement after prior treatment with a therapeutic.

"Refractory" refers to a disease that does not respond to a treatment. A refractory disease can be resistant to a treatment before or at the beginning of the treatment, or a refractory disease can become resistant during a treatment.

"**Drug substance**" or "**DS**" refers to any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish

pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or function of the body.

"**Drug product**" or "**DP**" refers to a finished dosage form, for example, a tablet, capsule or solution that contains an active pharmaceutical ingredient (e.g. drug substance), generally, but not necessarily, in association with inactive ingredients.

"**Wild-type BRAF**" refers to the serine/threonine protein kinase B-raf having an amino acid sequence shown in UniProt accession number P15056.

"**Mutant**" refers to a polypeptide or a polynucleotide that differs from a reference polypeptide or a reference polynucleotide by one or more modifications, for example one or more substitutions, insertions or deletions. For example, the reference BRAF polypeptide is the wild-type BRAF. Mutations are indicated using well-known numbering system, e.g. V600E refers to a substitution of glutamic acid for valine at position 600.

"**Immune condition**" or "**immune disorder**" encompasses, e.g., pathological inflammation, an inflammatory disorder, and an autoimmune disorder or disease. "Immune condition" also refers to infections, persistent infections, and proliferative conditions, such as cancer, tumors, and angiogenesis, including infections, tumors, and cancers that resist eradication by the immune system.

The invention provides a method of treating a cancer, comprising providing an antagonistic anti-PD1 antibody or an antigen binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 for administration at a dosage of between about 80 mg and about 1000 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks to a subject diagnosed with the cancer, and administering the antagonistic anti-PD-1 antibody to the subject diagnosed with the cancer.

The invention also provides a method of treating an immune condition, comprising providing an antagonistic anti-PD1 antibody or an antigen binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 for administration at a dosage of between about 80 mg and about 1000 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks to

a subject diagnosed with the immune condition, and administering the antagonistic anti-PD-1 antibody to the subject diagnosed with the cancer.

In some embodiments, the immune condition is a cancer.

In some embodiments, the immune condition is a viral infection, a persistent viral infection, inflammation, an inflammatory disorder or an autoimmune disorder or disease.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at a dosage of about 80 mg, about 160 mg, about 240 mg, about 320 mg, about 400 mg, about 480 mg, about 560 mg, about 720 mg, about 800 mg, about 880 mg or about 960 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

The invention also provides a method of treating a cancer, comprising administering to a subject diagnosed with the cancer an antagonistic anti-PD1 antibody or an antigen binding fragment thereof, comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 at a dose of between about 240 mg and about 480 mg.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

The invention also provides a method of treating an immune condition, comprising administering to a subject diagnosed with the immune condition an antagonistic anti-PD1 antibody or an antigen binding fragment thereof, comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 at a dose of between about 240 mg and about 480 mg.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at a dosage of about 240 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at the dosage of about 240 mg once every two weeks.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at the dosage of about 240 mg once every three weeks.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at the dosage of about 240 mg once every four weeks.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at the dosage of about 240 mg once every five weeks.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at the dosage of about 240 mg once every six weeks.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at the dosage of about 480 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at the dosage of about 480 mg once every two weeks.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at the dosage of about 480 mg once every three weeks.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at the dosage of about 480 mg once every four weeks.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at the dosage of about 480 mg once every five weeks.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at the dosage of about 480 mg once every six weeks.

Diagnosis and staging of cancers is conducted by an oncologist using established diagnostic criteria.

In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is an advanced solid tumor. "**Advanced solid tumor**" refers to metastatic, unresectable, Stage III or Stage IV solid tumor.

In some embodiments, the cancer is selected from the group consisting of a lung cancer, a non-small cell lung cancer (NSCLC), a melanoma, a head and neck cancer, a bladder cancer, a gastrointestinal cancer, a gastric cancer, a gastro-esophageal junction cancer, an esophageal cancer, a liver cancer, a colorectal cancer (CRC), a colon cancer, a gallbladder cancer, a biliary tract cancer, a bladder cancer, an ovarian cancer, a fallopian tube cancer, a cervical cancer, a peritoneal cancer, an endometrial cancer, a small cell lung cancer (SCLC), a breast cancer, a pancreatic cancer, a renal cell carcinoma, a liver cancer, a Merkel cell carcinoma, a primary mediastinal B-cell lymphoma (PMBCL), a Hodgkin's lymphoma, a non-Hodgkin's lymphoma, a

large diffuse B-cell cell lymphoma (DLBLC), a multiple myeloma, a glioblastoma, an urothelial cancer, a salivary cancer, a mesothelioma, an anal cancer, a prostate cancer, a basal cell carcinoma and an advanced cutaneous squamous cell carcinoma (CSCC), or any combination thereof.

In some embodiments, the cancer is selected from the group consisting of a thymus cancer, a non-small cell lung cancer (NSCLC), a small cell lung cancer (SCLC), a melanoma, a bladder cancer, a renal cancer, a gastric cancer, an esophageal cancer or a colorectal cancer (CRC).

In some embodiments, the cancer is the lung cancer.

In some embodiments, the cancer is the NSCLC

In some embodiments, the cancer is the melanoma.

In some embodiments, the cancer is the head and neck cancer.

In some embodiments, the cancer is the bladder cancer.

In some embodiments, the cancer is the gastrointestinal cancer.

In some embodiments, the cancer is the gastric cancer.

In some embodiments, the cancer is the gastro-esophageal junction cancer.

In some embodiments, the cancer is the esophageal cancer.

In some embodiments, the cancer is the liver cancer.

In some embodiments, the cancer is the CRC.

In some embodiments, the cancer is the colon cancer.

In some embodiments, the cancer is the gallbladder cancer.

In some embodiments, the cancer is the biliary tract cancer.

In some embodiments, the cancer is the ovarian cancer.

In some embodiments, the cancer is the fallopian tube cancer.

In some embodiments, the cancer is the cervical cancer.

In some embodiments, the cancer is the peritoneal cancer.

In some embodiments, the cancer is the endometrial cancer.

In some embodiments, the cancer is the SCLC.

In some embodiments, the cancer is the breast cancer.

In some embodiments, the cancer is the pancreatic cancer.

In some embodiments, the cancer is the renal cell carcinoma.

In some embodiments, the cancer is the Merkel cell carcinoma.

In some embodiments, the cancer is the PMBCL.

In some embodiments, the cancer is the Hodgkin’s lymphoma.

In some embodiments, the cancer is the non-Hodgkin's lymphoma.

In some embodiments, the cancer is the DLBLC.

In some embodiments, the cancer is the multiple myeloma.

In some embodiments, the cancer is the glioblastoma.

In some embodiments, the cancer is the urothelial cancer.

In some embodiments, the cancer is the salivary cancer.

In some embodiments, the cancer is the mesothelioma.

In some embodiments, the cancer is the anal cancer.

In some embodiments, the cancer is the prostate cancer.

In some embodiments, the prostate cancer is an adenocarcinoma.

In some embodiments, the prostate cancer is a metastatic prostate cancer.

In some embodiments, the prostate cancer has metastasized to rectum, lymph node or bone, or any combination thereof.

In some embodiments, the prostate cancer is relapsed or refractory prostate cancer.

In some embodiments, the prostate cancer is a castration resistant prostate cancer.

In some embodiments, the prostate cancer is sensitive to androgen deprivation therapy.

In some embodiments, the prostate cancer is insensitive to androgen deprivation therapy.

In some embodiments, the cancer is the CSCC.

In some embodiments, the cancer is the basal cell carcinoma.

In some embodiments, the cancer is the thymus cancer.

The invention also provides a method of treating a cancer, comprising administering to a subject diagnosed with the cancer an antagonistic anti-PD1 antibody or an antigen binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 at a dosage of between about 80 mg and about 1000 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks, wherein the subject is PD-1 axis naïve.

The invention also provides a method of treating a cancer, comprising administering to a subject diagnosed with the cancer an antagonistic anti-PD1 antibody or an antigen binding fragment thereof, comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5

and a LCDR3 of SEQ ID NO: 6 at a dose of between about 240 mg and about 480 mg, wherein the subject is PD-1 axis naïve.

The invention also provides a method of treating a cancer, comprising administering to a subject diagnosed with the cancer an antagonistic anti-PD1 antibody or an antigen binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 at a dosage of between about 80 mg and about 1000 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks, wherein the subject is PD-1 axis naïve and has received at least one prior therapeutic for the treatment of the cancer.

The invention also provides a method of treating a cancer, comprising administering to a subject diagnosed with the cancer an antagonistic anti-PD1 antibody or an antigen binding fragment thereof, comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 at a dose of between about 240 mg and about 480 mg, wherein the subject has received one, two, three or more prior therapeutics to treat the cancer.

The invention also provides a method of treating a cancer, comprising administering to a subject diagnosed with the cancer an antagonistic anti-PD1 antibody or an antigen binding fragment thereof, comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 at a dose of between about 240 mg and about 480 mg, wherein the subject is PD-1 axis naïve and has received one, two, three or more prior therapeutics to treat the cancer.

"**PD-1 axis naïve**" refers to a subject who has not been treated with PD-1, PD-L1 or PD-L2 antagonists. Exemplary PD-1, PD-L1 or PD-L2 antagonists are nivolumab (OPDIVO®), pembrolizumab (KEYTRUDA®), cemiplimab (Libtayo®), sintilimab, tislelizumab, tripolibamab durvalumab (IMFINZI®), atezolizumab (TECENTRIQ®), avelumab (BAVENCIO®) or envafolimab, or any other PD-1, PD-L1 or PD-L2 antagonist. Additional such antagonists are known and include those listed for example at Citeline PharmaIntelligence website.

In some embodiments, the cancer is PD-L1 positive.

In some embodiments, the cancer is PD-L1 high.

In some embodiments, PD-L1 expression in the cancer is undetermined.

"**PD-L1 positive**" refers to a tumor in which at least about 1% of the cells in a sample obtained from the tumor (such as a paraffin embedded formalin fixed tumor tissue sample) comprising of tumor cells and tumor-infiltrating inflammatory cells stain positive for PD-L1 surface expression.

"**PD-L1 high**" refers to a tumor in which at least 50% of the tumor cells or tumor-infiltrating inflammatory cells in a sample obtained from the tumor (such as a paraffin embedded formalin fixed tumor tissue sample) stain positive for PD-L1 surface expression. Commercial kits from for example from Ventana, DAKO or PharmDx may be used to assess PD-L1 positive or PD-L1 high status. In these assays, PD-L1 expression on tumor cell membrane is evaluated using anti-PD-L1 antibodies such as 28-8, 22C3, SP142, SP263 and 73-10, and a Tumor Proportion Score (TPS) indicative of percentage of PD-L1 positive tumor cells is calculated.

"**PD-L1 expression in the cancer is undetermined**" refers to a tumor in which PD-L1 surface expression has not been assessed.

In some embodiments, the cancer expresses a mutant BRAF.

In some embodiments, the mutant BRAF comprises a V600E mutation.

In some embodiments, the cancer expresses a wild-type BRAF.

In some embodiments, the mutant BRAF comprises one or more mutations selected from the group consisting of: V600E, V600L, R462I, 1463 S, G464E, G464R, G464V, G466A, G469A, N581 S, E586K, F595L, L597Q, L597R, L597S, L597V, A598V, T599E, V600R, K601E, S602D and A728V, and any combination thereof (see e.g. Int. Pat. Publ. No. WO2018/213302).

Mitogen-activated protein kinase (MAPK) or RAS/RAF/MEK/ERK signaling is responsible for several cell signaling pathways involved in control of proliferation, differentiation, and apoptosis. Activating mutations of the serine-threonine kinase BRAF gene is the most frequent genetic alteration in melanomas; the BRAF mutation is observed in about 50% of skin melanoma and in about 10-20% of mucosal melanoma cases (MacKiewicz and Mackiewicz, *Contem Oncol* 22:68-72, 2018). Treatment of patients harboring BRAF mutations with BRAF inhibitors (such as vemurafenib, dabrafenib and encorafenib) is associated with acquired resistance to treatment and hence MEK inhibitor such as cobimetinib, trametinib or binimetinib may be combined to the treatment regimen. MEK inhibitors have also been tested as monotherapy in BRAF mutant subjects.

BRAF status may be assessed for example from tumor biopsy samples using known methods such as sequencing.

In some embodiments, the subject has received or is ineligible to receive at least one prior therapeutic to treat the cancer.

In some embodiments, the subject has received one, two, three or more prior therapeutics to treat the cancer.

Therapeutics to treat various cancers are known, and include surgery, radiation therapy, chemotherapy, hormone therapy, immunotherapy, targeted therapy or any combination thereof.

Therapeutics to treat lung cancer, such as a non-small cell lung cancer (NSCLC) or a small cell lung cancer (SCLC) include methotrexate, paclitaxel (ABRAXANE®), afatinib (GILOTRIF®), everolimus (AFINITOR®), alectinib (ALECENSA®), pemetrexed disodium (ALIMTA®), bevacizumab (AVASTIN®), carboplatin, ceritinib (ZYKADIA®), crizotinib (XALKORI®), ramucirumab (CYRAMZA®), docetaxel, everolimus (AFINITOR®), gefitinib (IRESSA®), gemcitabine hydrochloride (GMEZAR®), pembrolizumab (KEYTRUDA®), mechlorethamine hydrochloride (MUSTARGEN®), vinorelbine tartrate (NAVELBINE®), necitumumab (PORTRAZZA®), nivolumab (OPDIVO®), carboplatin, pemetrexed disodium, ramucirumab (CYRAMZA®), osimertinib (TAGRISSO®), an anti-CTLA4 antibody, a BRAF/MEK inhibitor or interferon alpha. An exemplary anti-CTLA4 antibody is ipilimumab (YERVOY®). Exemplary BRAF/MEK inhibitors are vemurafenib (ZELBORAF®), dabrafenib, encorafenib, cobimetinib (COTELLIC®), trametinib (MEKINIST®), and binimetinib.

Therapeutics to treat melanoma include Aldesleukin, cobimetinib (COTELLIC®), dabrafenib (TAFINLAR®), dacarbazine (DTIC-Dome®), talimogene laherparepvec (IMLYGIC®), ipilimumab (YERVOY®), pembrolizumab (KEYTRUDA®), trametinib (MEKINIST®), nivolumab (OPDIVO®), Peginterferon Alfa-2b (PEG-INTRON®, SYLATRON®), recombinant interferon Alfa-2b and vemurafenib (ZELBORAF®).

Therapeutics to treat a bladder cancer include surgery, chemotherapy (such as cisplatin, gemcitabine, carboplatin, methotrexate, vinblastine, doxorubicin or any combination thereof), immunotherapy (such as weakened bacterium bacillus Calmette-Guerin (BCG), interferon, atezolizumab (TECENTRIQ®), nivolumab (OPDIVO®), durvalumab (IMFINZI®), avelumab (BAVENCIO®), or pembrolizumab (KEYTRUDA®) or radiation therapy. Therapeutics to treat a renal cancer include everolimus (AFINITOR®), aldesleukin, bevacizumab (AVASTIN®), axitinib (INLYTA®), cabozantinib-S-Malate (CABOMETYX®), aldesleukin (PROLEUKIN®), lenvatinib mesylate (LENVIMA®), sorafenib tosylate (NEXAVAR®), nivolumab (OPDIVO®), pazopanib hydrochloride, sorafenib tosylate, sunitinib (SUTENT®), temsirolimus (TORISEL®) and pazopanib hydrochloride (VOTRIENT®).

Therapeutics to treat a gastric cancer include surgery or chemotherapy (such as 5-fluorouracil or capecitabine, irinotecan, docetaxel or paclitaxel, or any combination thereof). Therapeutics to treat an esophageal cancer include surgery, endoscopic therapy, radiation therapy, chemotherapy or targeted immunotherapy.

Therapeutics to treat a colorectal cancer (CRC) include 5-fluorouracil and leucovorin, capecitabine (XELODA®), irinotecan (CAMPTOSAR®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), pegorafenib (STIVARGA®), a chemotherapy regimen of trifluridine and tiptracil (LONSURF®), FOLFOX: chemotherapy regimen of leucovorin, 5-fluorouracil and oxaliplatin (ELOXATIN®), FOLFIRI: chemotherapy regimen of leucovorin, 5-fluorouracil, and irinotecan (CAMPTOSAR®), CapeOX: chemotherapy regimen of capecitabine (XELODA®) and oxaliplatin (ELOXATIN®), FOLFOXIRI: chemotherapy regimen of leucovorin, 5-fluorouracil, oxaliplatin (ELOXATIN®), and irinotecan (CAMPTOSAR®), or any of the above individual agents or chemotherapy regiments in combination with each other or in combination with a drug that targets VEGF such as bevacizumab (AVASTIN®), ziv-aflibercept (ZALTRAP®) or ramucirumab (CYRAMZA®).

Therapeutics to treat thymus cancer include surgery, radiation therapy, a chemotherapy (such as carboplatin, cisplatin, cyclophosphamide, doxorubicin, etoposide, ifosfamide, octreotide, paclitaxel or pemetrexed, or any combination thereof) or a hormone therapy (such as corticosteroids).

Radiation therapy includes external beam radiation, intensity modulated radiation therapy (IMRT), focused radiation, and any form of radiosurgery including Gamma Knife, Cyberlaiife, Linac, and interstitial radiation (for example implanted radioactive seeds, GliaSite balloon), and/or with surgery.

Focused radiation methods that may be used include stereotactic radiosurgery, fractionated stereotactic radiosurgery, and intensity-modulated radiation therapy (IMRT). It is apparent that stereotactic radiosurgery involves the precise delivery of radiation to a tumorous tissue, while avoiding the surrounding non-tumorous, normal tissue. The dosage of radiation applied using stereotactic radiosurgery may vary typically from 1 Gy to about 30 Gy, and may encompass intermediate ranges including, for example, from 1 to 5, 10, 15, 20, 25, up to 30 Gy in dosage. Because of noninvasive fixation devices, stereotactic radiation need not be delivered in a single treatment. The treatment plan may be reliably duplicated day-to-day, thereby allowing multiple fractionated dosages of radiation to be delivered. When used to treat a tumor over time, the radiosurgery is referred to as “fractionated stereotactic radiosurgery” or FSR. In contrast, stereotactic radiosurgery refers to a one-session treatment. Fractionated stereotactic radiosurgery

may result in a high therapeutic ratio, i.e., a high rate of killing of tumor cells and a low effect on normal tissue. The tumor and the normal tissue respond differently to high single dosages of radiation vs. multiple smaller dosages of radiation. Single large dosages of radiation may kill more normal tissue than several smaller dosages of radiation may. Accordingly, multiple smaller dosages of radiation can kill more tumor cells while sparing normal tissue. The dosage of radiation applied using fractionated stereotactic radiation may vary from range from 1 Gy to about 50 Gy, and may encompass intermediate ranges including, for example, from 1 to 5, 10, 15, 20, 25, 30,40, up to 50 Gy in hypofractionated dosages. Intensity- modulated radiation therapy (IMRT) may also be used. IMRT is an advanced mode of high-precision three-dimensional conformal radiation therapy (3DCRT), which uses computer-controlled linear accelerators to deliver precise radiation dosages to a malignant tumor or specific areas within the tumor, the profile of each radiation beam is shaped to fit the profile of the target from a beam's eye view (BEV) using a multileaf collimator (MLC), thereby producing a number of beams. IMRT allows the radiation dosage to conform more precisely to the three-dimensional (3-D) shape of the tumor by modulating the intensity of the radiation beam in multiple small volumes. Accordingly, IMRT allows higher radiation dosages to be focused to regions within the tumor while minimizing the dosage to surrounding normal critical structures. IMRT improves the ability to conform the treatment volume to concave tumor shapes, for example, when the tumor is wrapped around a vulnerable structure, such as the spinal cord or a major organ or blood vessel. Suitable radiation sources for use as a cell conditioner include both solids and liquids.

In some embodiments the one, two, three or more prior therapeutics to treat the cancer are an anti-CTLA4 antibody, ipilimumab (YERVOY®), BRAF/MEK inhibitor, chemotherapy or interferon alpha, or any combination thereof.

"**BRAF/MEK inhibitor**" refers to a molecule, such as a small molecule, that inhibits at least one biological activity mediated by BRAF and/or MEK. The inhibition may be at least about 20%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% greater than in the absence of the inhibitor (*e.g.,* negative control), or when the inhibition is statistically significant when compared to a control. Typical biological activities mediated by BRAF and/or MEK are protein phosphorylation, cell proliferation, cell survival and apoptosis, which can be measured using standard methods.

Exemplary BRAF inhibitors are vemurafenib (ZELBORAF®), pazopanib, dabrafenib and encorafenib.

Exemplary MEK inhibitors are cobimetinib (COTELLIC®), trametinib (MEKINIST®), and binimetinib.

In some embodiments, the subject is resistant, refractory or resistant and refractory to the one, two, three or more prior therapeutics to treat the cancer, or any combination thereof.

In some embodiments, the subject is resistant, refractory or resistant and refractory to an anti-CTLA4 antibody, ipilimumab, BRAF/MEK inhibitor, chemotherapy or interferon alpha, or any combination thereof.

Various qualitative and/or quantitative methods may be used to determine relapse or refractory nature of the disease. Symptoms that may be associated with relapse or resistance are, for example, a decline or plateau of the well-being of the patient or re-establishment or worsening of various symptoms associated with solid tumors, and/or the spread of cancerous cells in the body from one location to other organs, tissues or cells.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered or provided for administration in a pharmaceutical composition comprising between about 10 mg/ml to about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients.

"**Pharmaceutically acceptable excipients**" refer to solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible, such as salts, buffers, antioxidants, saccharides, aqueous or non-aqueous carriers, preservatives, wetting agents, surfactants or emulsifying agents, or combinations thereof.

Exemplary buffers that may be used are acetic acid, citric acid, formic acid, succinic acid, phosphoric acid, carbonic acid, malic acid, aspartic acid, histidine, boric acid, Tris buffers, HEPPSO and HEPES.

Exemplary antioxidants that may be used are ascorbic acid, methionine, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite, lecithin, citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol and tartaric acid.

Exemplary amino acids that may be used are histidine, isoleucine, methionine, glycine, arginine, lysine, L-leucine, tri-leucine, alanine, glutamic acid, L-threonine, and 2-phenylamine.

Exemplary surfactants that may be used are polysorbates (e.g., polysorbate-20 or polysorbate-80); polyoxamers (e.g., poloxamer 188); Triton; sodium octyl glycoside; lauryl-, myristyl-, linoleyl-, or stearyl-sulfobetaine; lauryl-, myristyl-, linoleyl- or stearyl-sarcosine; linoleyl-, myristyl-, or cetyl-betaine; lauroamidopropyl-, cocamidopropyl-, linoleamidopropyl-, myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-betaine (e.g., lauroamidopropyl); myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-dimethylamine; sodium methyl cocoyl-, or disodium methyl oleyl-taurate; and the MONAQUA™ series (Mona Industries, Inc.,

Paterson, N.J.), polyethyl glycol, polypropyl glycol, and copolymers of ethylene and propylene glycol (e.g., PLURONICS™, PF68, etc).

Exemplary preservatives that may be used are phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof.

Exemplary saccharides that may be used are monosaccharides, disaccharides, trisaccharides, polysaccharides, sugar alcohols, reducing sugars, nonreducing sugars such as glucose, sucrose, trehalose, lactose, fructose, maltose, dextran, glycerin, dextran, erythritol, glycerol, arabitol, sylitol, sorbitol, mannitol, mellibiose, melezitose, raffinose, mannotriose, stachyose, maltose, lactulose, maltulose, glucitol, maltitol, lactitol or iso-maltulose.

Exemplary salts that may be used are acid addition salts and base addition salts. Acid addition salts include those derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorous and the like, as well as from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the like. Base addition salts include those derived from alkaline earth metals, such as sodium, potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such as N,N′-dibenzylethylenediamine, N-methylglucamine, chloroprocaine, choline, diethanolamine, ethylenediamine, procaine and the like. An exemplary salt is sodium chloride.

The amounts of pharmaceutically acceptable carrier(s) in the pharmaceutical compositions may be determined experimentally based on the activities of the carrier(s) and the desired characteristics of the formulation, such as stability and/or minimal oxidation.

In some embodiments, the pharmaceutical composition comprises histidine.

In some embodiments, the pharmaceutical composition comprises histidine at a concentration of from about 1 mM to about 50 mM.

In some embodiments, the pharmaceutical composition comprises histidine at a concentration of from about 5 mM to about 50 mM.

In some embodiments, the pharmaceutical composition comprises histidine at a concentration of from about 5 mM to about 30 mM.

In some embodiments, the pharmaceutical composition comprises histidine at a concentration of from about 5 mM to about 20 mM.

In some embodiments, the pharmaceutical composition comprises histidine at a concentration of from about 5 mM to about 15 mM.

In some embodiments, the pharmaceutical composition comprises histidine at a concentration of from about 5 mM to about 10 mM.

In some embodiments, the pharmaceutical composition comprises histidine at a concentration of about 1 mM, about 2 mM, about 3 mM, about 4 mM, about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, about 20 mM, about 21 mM, about 22 mM, about 23 mM, about 24 mM, about 25 mM, about 26 mM, about 27 mM, about 28 mM, about 29 mM, about 30 mM, about 31 mM, about 32 mM, about 33 mM, about 34 mM, about 35 mM, about 36 mM, about 37 mM, about 38 mM, about 39 mM, about 40 mM, about 41 mM, about 42 mM, about 43 mM, about 44 mM, about 45 mM, about 46 mM, about 47 mM, about 48 mM, about 49 mM or about 50 mM.

In some embodiments, the pharmaceutical composition comprises histidine at a concentration of about 10 mM.

In some embodiments, the pharmaceutical composition comprises sucrose.

In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of from about 1% (w/v) to about 20% (w/v).

In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of from about 2% (w/v) to about 18% (w/v).

In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of from about 4% (w/v) to about 16% (w/v).

In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of from about 6% (w/v) to about 14% (w/v).

In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of from about 6% (w/v) to about 12% (w/v).

In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of from about 6% (w/v) to about 10% (w/v).

In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of about 1% (w/v), about 2% (w/v), about 3% (w/v), about 4% (w/v), about 5% (w/v), about 6% (w/v), about 7% (w/v), about 8% (w/v), about 9% (w/v), about 10% (w/v), about 11% (w/v), about 12% (w/v), about 13% (w/v), about 14% (w/v), about 15% (w/v), about 16% (w/v), about 17% (w/v), about 18% (w/v), about 19% (w/v) or about 20% (w/v),

In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of about 8% (w/v).

In some embodiments, the pharmaceutical composition comprises polysorbate-20.

In some embodiments, the pharmaceutical composition comprises polysorbate-20 (PS-20) at a concentration of from about 0.01% (w/v) to about 0.1% (w/v).

In some embodiments, the pharmaceutical composition comprises polysorbate-20 (PS-20) at a concentration of from about 0.01% (w/v) to about 0.08% (w/v).

In some embodiments, the pharmaceutical composition comprises polysorbate-20 (PS-20) at a concentration of from about 0.02% (w/v) to about 0.06% (w/v).

In some embodiments, the pharmaceutical composition comprises polysorbate-20 (PS-20) at a concentration of about 0.01% (w/v), about 0.02% (w/v), about 0.03% (w/v), about 0.04% (w/v), about 0.05% (w/v), about 0.06% (w/v), about 0.07% (w/v), about 0.08% (w/v), about 0.09% (w/v) or about 0.1% (w/v).

In some embodiments, the pharmaceutical composition comprises polysorbate-20 (PS-20) at a concentration of about 0.04% (w/v).

In some embodiments, the pharmaceutical composition comprises EDTA.

In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of from about 1 μg/ml to about 50 μg/ml.

In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of from about 5 μg/ml to about 50 μg/ml.

In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of from about 5 μg/ml to about 30 μg/ml.

In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of from about 5 μg/ml to about 20 μg/ml.

In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of from about 5 μg/ml to about 15 μg/ml.

In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of from about 5 μg/ml to about 10 μg/ml.

In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of about 1 μg/ml, about 2 μg/ml, about 3 μg/ml, about 4 μg/ml, about 5 μg/ml, about 6 μg/ml, about 7 μg/ml, about 8 μg/ml, about 9 μg/ml, about 10 μg/ml, about 11 μg/ml, about 12 μg/ml, about 13 μg/ml, about 14 μg/ml, about 15 μg/ml, about 16 μg/ml, about 17 μg/ml, about 18 μg/ml, about 19 μg/ml, about 20 μg/ml, about 21 μg/ml, about 22 μg/ml, about

23 μg/ml, about 24 μg/ml, about 25 μg/ml, about 26 μg/ml, about 27 μg/ml, about 28 μg/ml, about 29 μg/ml, about 30 μg/ml, about 31 μg/ml, about 32 μg/ml, about 33 μg/ml, about 34 μg/ml, about 35 μg/ml, about 36 μg/ml, about 37 μg/ml, about 38 μg/ml, about 39 μg/ml, about 40 μg/ml, about 41 μg/ml, about 42 μg/ml, about 43 μg/ml, about 44 μg/ml, about 45 μg/ml, about 46 μg/ml, about 47 μg/ml, about 48 μg/ml, about 49 μg/ml or about 50 μg/ml.

In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of about 20 μg/ml.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered or provided for administration in a pharmaceutical composition comprising between about 10 mg/ml to about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, histidine, sucrose, polysorbate-20 and EDTA.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered or provided for administration in a pharmaceutical composition comprising between about 10 mg/ml to about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 μg/ml EDTA at pH 6.5.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered or provided for administration in a pharmaceutical composition comprising about 10 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 μg/ml EDTA at pH 6.5.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered or provided for administration in a pharmaceutical composition comprising about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 μg/ml EDTA at pH 6.5.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is provided for administration as a lyophilized formulation comprising between about 90 mg and about 240 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is provided for administration as a lyophilized formulation comprising about 90 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is provided for administration as a lyophilized formulation comprising about 240 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients.

In some embodiments, the lyophilized formulation, once reconstituted, comprises about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

In some embodiments, the pharmaceutical composition is a liquid.

In some embodiments, the pharmaceutical composition is a frozen liquid.

In some embodiments, the pharmaceutical composition is a lyophilized powder.

In some embodiments, the pharmaceutical composition is provided in a volume of between about 1 ml to about 20 ml.

In some embodiments, the pharmaceutical composition is provided in a volume of about 1 ml, about 2 ml, about 3 ml, about 4 ml, about 5 ml, about 6 ml, about 7 ml, about 8 ml, about 9 ml, about 10 ml, about 11 ml, about 12 ml, about 13 ml, about 14 ml, about 15 ml, about 16 ml, about 17 ml, about 18 ml, about 19 ml or about 20 ml.

In some embodiments, the pharmaceutical composition is provided or reconstituted in a volume of about 3 ml.

In some embodiments, the pharmaceutical composition is provided or reconstituted in a volume of about 3.3 ml.

In some embodiments, the pharmaceutical composition is provided or reconstituted in a volume of about 8 ml.

In some embodiments, the pharmaceutical composition is provided or reconstituted in a volume of about 8.6 ml.

In some embodiments, the pharmaceutical composition is provided or reconstituted in a volume of about 8.8 ml.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered or provided for administration in a pharmaceutical composition comprising about 10 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5 in a volume of about 3.3 ml.

In some embodiments, the antagonistic anti-PD-1 antibody is cetrelimab. Cetrelimab is an IgG4/κ antibody characterized by following amino acid sequences: the HCDR1 of SEQ ID

NO: 1, the HCDR2 of SEQ ID NO: 2, the HCDR3 of SEQ ID NO: 3, the LCDR1 of SEQ ID NO: 4, the LCDR2 of SEQ ID NO: 5, the LCDR6 of SEQ ID NO: 6, the VH of SEQ ID NO: 7, the VL of SEQ ID NO: 8, the HC of SEQ ID NO: 9 and the LC of SEQ ID NO: 10.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered or provided for administration as a lyophilized formulation comprising about 90 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients that upon reconstitution into about 3.3 ml comprises about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

In some embodiments, the antagonistic anti-PD-1 antibody is cetrelimab.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered or provided for administration as a lyophilized formulation comprising about 240 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients that upon reconstitution into about 8.6 ml comprises about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

In some embodiments, the antagonistic anti-PD-1 antibody is cetrelimab.

"**Lyophilization**," "**lyophilized**," and "**freeze-dried**" refer to a process by which the material to be dried is first frozen and then the ice or frozen solvent is removed by sublimation in a vacuum environment. An excipient may be included in pre-lyophilized formulations to enhance stability of the lyophilized product upon storage.

"**Reconstitute**", "**reconstituted**" or "**reconstitution**" refers to dissolving the lyophilized formulation in a diluent so that the protein in the lyophilized formulation is dispersed in the reconstituted formulation. The reconstituted formulation is suitable for administration, e.g. parenteral administration), and may optionally be suitable for subcutaneous administration. In some embodiments, the diluent is sterile water for injection (sWFI).

"**Pharmaceutical composition**", "**pharmaceutical formulation** "or "**formulation**" refers to a combination of an active ingredient (e.g. the anti-PD-1 antibody) and one or more excipients in either liquid or solid (*e.g.* lyophilized) form.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered by an intravenous infusion.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is diluted into a volume of between about 100 ml and 1000 ml prior to administration.

In some embodiments, duration of the intravenous infusion is between about 20 minutes and about 80 minutes.

In some embodiments, duration of the intravenous infusion is about 20, about 30, about 40, about 50, about 60, about 70 or about 80 minutes.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered by one or more subcutaneous injections.

The invention also provides a method of treating a cancer, comprising administering to a subject diagnosed with the cancer an antagonistic anti-PD1 antibody or an antigen binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 at a dosage of between about 80 mg and about 1000 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks, wherein the subject is PD-1 axis naïve, has received and/or is ineligible for at least one prior therapeutic for the treatment of the cancer, or any combination thereof.

In some embodiments, the method achieves an overall response rate (ORR) of at least 15% in a group of subjects diagnosed with the cancer. ORR is defined as a percentage of subjects achieving partial response (PR) or complete response (CR). ORR may be assessed per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or per irRC in subjects with selected advanced solid tumors (irRC = – IRRC = Immune-Related Response Criteria from Wolchok *et al.* (2009) *Clin Cancer Res* 15: 7412-20).

In some embodiments, the ORR of at least about 15% is achieved after a median duration of treatment of about 1 ½ months or more.

In some embodiments, the ORR of at least about 15% is achieved after a median duration of treatment of about 1 months or more, about 2 months or more, about 3 months or more, about 4 months or more, about 5 months or more, about 6 months or more, about 7 months or more, about 8 months or more, about 9 months or more, about 10 months or more, about 11 months or more, or about 12 months or more.

In some embodiments, the method achieves an ORR of at least about 19% in the group of subjects diagnosed with the cancer.

In some embodiments, the cancer is the NSCLC.

In some embodiments, the method achieves an ORR of at least about 30% in a group of subjects diagnosed with PD-L1 high NSCLC or an ORR of at least about 25% in a group of subjects whose PD-L1 expression in the cancer is undetermined.

In some embodiments, the method achieves an ORR of at least about 35% in the group of subjects diagnosed with PD-L1 high NSCLC.

In some embodiments, the cancer is the melanoma.

In some embodiments, the method achieves or an ORR of at least about 25% in a group of subjects diagnosed with melanoma.

In some embodiments, the melanoma is a non-uveal melanoma.

In some embodiments, the method achieves an ORR of at least about 30% in a group of subjects diagnosed with the non-uveal melanoma.

In some embodiments, the method achieves an ORR of at least about 35% in a group of subjects diagnosed with MSI-H CRC.

In some embodiments, the method achieves an ORR of at least about 35% in a group of subjects diagnosed with dMMR CRC.

The invention also provides a method of treating a colorectal cancer (CRC), comprising administering to a subject diagnosed with the CRC an antagonistic anti-PD1 antibody or an antigen binding fragment thereof comprising a HCDR1 of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a LCDR1 of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 for a time sufficient to treat the CRC.

The invention also provides a method of treating a mismatch repair-deficient (dMMR) colorectal cancer (CRC) or high-level microsatellite instability (MSI-H) CRC, comprising administering to a subject diagnosed with the dMMR CRC or MSI-H CRC an antagonistic anti-PD1 antibody or an antigen binding fragment thereof comprising a HCDR1 of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a LCDR1 of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 for a time sufficient to treat the dMMR CRC or the MSI-H CRC.

Approximately 15 % of colorectal carcinomas (CRC) have deficient DNA mismatch repair (dMMR) which is characterized by microsatellite instability (MSI) in the tumor. Tumors with the dMMR/MSI result typically from germline mutation in one of the MMR genes or somatic inactivation of the same pathway. dMMR/MSI tumors include hereditary non-polyposis colorectal cancer (HNPCC), also called Lynch syndrome and sporadic MSI-H CRC. Lynch syndrome is caused by germline mutations in MMR genes MLH1, MSH2, MSH6 or PMS2, or epigenetic inactivation of MSH2. Sporadic MSI-H CRCs are frequently caused by methylation of

MLH1 promoter. A subset of MSI-H tumors has no alterations in the MMR genes themselves, but instead overexpress various miRNAs that may silence the MMR genes. For example, miRNA-21 found overexpressed in MSI-H CRC targets MSH2 and MSH6 mRNA.

MSI-H CRC can be detected using polymerase chain reaction (PCR) of tumor tissue samples detecting stability of microsatellite markers. CRC is classified as MSI-H if instability is shown in 30% or more of microsatellite markers with at least 5 markers evaluated. The National Cancer Institute has recommended a panel of 5 microsatellites for MSI screening: BAT25 and BAT26 (mononucleotide repeats), D2S123, D5S346, and D17S250 (dinucleotide repeats). dMMR can be detected using immunohistochemistry of tumor tissues. CRC is classified as dMMR if loss of at least one MMR genes MLH1, MSH2, MSH6 or PMS2 is detected in the tumor tissue.

In some embodiments, the CRC is a stage II CRC or a stage III CRC. CRC staging is known, using for example the American Joint Committee on Cancer (AJCC) TNM system and diagnosis by an oncologist.

In some embodiments, the subject diagnosed with CRC is refractory to treatment with fluoropyrimidine, oxaliplatin or irinotecan, or any combination thereof.

In some embodiments, the subject diagnosed with CRC has a relapsed tumor after treatment with fluoropyrimidine, oxaliplatin or irinotecan, or any combination thereof.

Various qualitative and/or quantitative methods may be used to determine relapse or refractory nature of the disease. Symptoms that may be associated with relapse or refractory disease are, for example, a decline or plateau of the well-being of the patient or re-establishment or worsening of various symptoms associated with tumors, and/or the spread of cancerous cells in the body from one location to other organs, tissues or cells.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody or an antigen binding fragment thereof comprising a HCDR1 of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a LCDR1 of SEQ ID NO: 4, a LCDR2 or SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 for a time sufficient to treat the thymus cancer.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody or an antigen binding fragment thereof comprising a heavy chain variable region (VH) of SEQ ID NO: 7 and a light chain variable region (VL) of SEQ ID NO: 8 for a time sufficient to treat the thymus cancer.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody comprising a heavy chain (HC) of SEQ ID NO: 9 and a light chain (LC) of SEQ ID NO: 10 for a time sufficient to treat the thymus cancer.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody comprising a heavy chain (HC) of SEQ ID NO: 9 and a light chain (LC) of SEQ ID NO: 10 at a dosage of between about 80 mg and about 1000 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody comprising a heavy chain (HC) of SEQ ID NO: 9 and a light chain (LC) of SEQ ID NO: 10 at a dosage of about 80 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody comprising a heavy chain (HC) of SEQ ID NO: 9 and a light chain (LC) of SEQ ID NO: 10 at a dosage of about 160 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody comprising a heavy chain (HC) of SEQ ID NO: 9 and a light chain (LC) of SEQ ID NO: 10 at a dosage of about 240 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody comprising a heavy chain (HC) of SEQ ID NO: 9 and a light chain (LC) of SEQ ID NO: 10 at a dosage of about 320 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody comprising a heavy chain (HC) of SEQ ID NO: 9 and a light chain (LC) of SEQ ID NO: 10 at a dosage of about 400 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody comprising a heavy chain (HC) of SEQ ID NO: 9 and a light chain (LC) of SEQ ID NO: 10 at a dosage of about 480 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody comprising a heavy chain (HC) of SEQ ID NO: 9 and a light chain (LC) of SEQ ID NO: 10 at a dosage of about 560 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody comprising a heavy chain (HC) of SEQ ID NO: 9 and a light chain (LC) of SEQ ID NO: 10 at a dosage of about 720 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody comprising a heavy chain (HC) of SEQ ID NO: 9 and a light chain (LC) of SEQ ID NO: 10 at a dosage of about 800 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody comprising a heavy chain (HC) of SEQ ID NO: 9 and a light chain (LC) of SEQ ID NO: 10 at a dosage of about 880 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

The invention also provides a method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody comprising a heavy chain (HC) of SEQ ID NO: 9 and a light chain (LC) of SEQ ID NO: 10 at a dosage of about 960 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

In some embodiments, the thymus cancer is a thymoma.

In some embodiments, the thymoma is a type A thymoma.

In some embodiments, the thymoma is a type AB thymoma.

In some embodiments, the thymoma is a type B1 thymoma.

In some embodiments, the thymoma is a type B2 thymoma.

In some embodiments, the thymoma is a type B3 thymoma.

In some embodiments, the thymus cancer is a thymic carcinoma.

In some embodiments, the thymic carcinoma is a low grade thymic carcinoma.

In some embodiments, the thymic carcinoma is high grade thymic carcinoma.

In some embodiments, the thymus cancer is a metastatic thymic cancer.

In some embodiments, the thymus cancer has metastasized to lung, lymph node, heart or bone.

In some embodiments, the subject has been treated with surgery, radiation therapy, a chemotherapy or a hormone therapy.

In some embodiments, the subject has been treated with carboplatin, cisplatin, cyclophosphamide, doxorubicin, etoposide, ifosfamide, octreotide, paclitaxel or pemetrexed, or any combination thereof.

Thymus cancer may be staged for example according to the American Society of Clinical Oncology (ASCO) staging system.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof comprises a heavy chain variable region (VH) of SEQ ID NO: 7 and a light chain variable region (VL) or SEQ ID NO: 8.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is an IgG1, an IgG2, and IgG3 or an IgG4 isotype.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is an IgG4 isotype.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is an IgG4 isotype and comprises proline at position 228, residue numbering according to the EU Index.

In some embodiments, the antagonistic anti-PD-1 antibody is a nG4m(a) allotype.

In some embodiments, the antagonistic anti-PD-1 antibody or an antigen binding fragment thereof has at least one substitution in an Fc region to modulate antibody effector functions or antibody half-life.

In some embodiments, the antagonistic anti-PD-1 antibody comprises a heavy chain of SEQ ID NO: 9 and a light chain of SEQ ID NO: 10.

The invention also provides a pharmaceutical composition comprising about 10 mg/ml of the antagonistic anti-PD-1 antibody comprising the HC of SEQ ID NO: 9 and the LC of SEQ ID

NO: 10, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate 20 and about 20 µg/ml and EDTA at pH 6.5.

SEQ ID NO: 1

SYAIS

SEQ ID NO: 2

GIIPIFDTANYAQKFQG

SEQ ID NO: 3

PGLAAAYDTGSLDY

SEQ ID NO: 4

RASQSVRSYLA

SEQ ID NO: 5

DASNRAT

SEQ ID NO: 6

QQRNYWPLT

SEQ ID NO: 7

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFDTAN
YAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARPGLAAAYDTGSLDYWGQGT
LVTVSS

SEQ ID NO: 8

EIVLTQSPATLSLSPGERATLSCRASQSVRSYLAWYQQKPGQAPRLLIYDASNRATGIPAR
FSGSGSGTDFTLTISSLEPEDFAVYYCQQRNYWPLTFGQGTKVEIK

SEQ ID NO: 9

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFDTAN
YAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARPGLAAAYDTGSLDYWGQGT
LVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA

VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFL
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE
QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPS
QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD
KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO: 10

EIVLTQSPATLSLSPGERATLSCRASQSVRSYLAWYQQKPGQAPRLLIYDASNRATGIPAR
FSGSGSGTDFTLTISSLEPEDFAVYYCQQRNYWPLTFGQGTKVEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS
KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

The invention also provides a pharmaceutical composition comprising

between about 10 mg/ml and about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

about 10 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

a lyophilized formulation comprising between about 90 mg and about 240 mg of cetrelimab and one or more pharmaceutically acceptable excipients;

a lyophilized formulation comprising about 90 mg of cetrelimab and one or more pharmaceutically acceptable excipients; or

a lyophilized formulation comprising about 240 mg of cetrelimab and one or more pharmaceutically acceptable excipients.

In some embodiments, the lyophilized formulation, once reconstituted, comprises about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

The invention also provides a drug product comprising

between about 10 mg/ml and about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

about 10 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

a lyophilized formulation comprising between about 90 mg and about 240 mg of cetrelimab and one or more pharmaceutically acceptable excipients;

a lyophilized formulation comprising about 90 mg of cetrelimab and one or more pharmaceutically acceptable excipients; or

a lyophilized formulation comprising about 240 mg of cetrelimab and one or more pharmaceutically acceptable excipients.

In some embodiments, the lyophilized formulation, once reconstituted, comprises about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

In some embodiments, the lyophilized formulation is reconstituted into sterile water for injection (sWFI).

The invention also provides a drug product comprising about 10 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5 in a volume of about 3.3 ml.

The invention also provides a drug product comprising a lyophilized formulation comprising about 90 mg cetrelimab that upon reconstitution into about 3.3 ml comprises about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

The invention also provides a drug product comprising a lyophilized formulation comprising about 240 mg cetrelimab that upon reconstitution into about 8.6 ml comprises about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

The invention also provides a drug product comprising

between about 10 mg/ml and about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

about 10 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

a lyophilized formulation comprising between about 90 mg and about 240 mg of cetrelimab and one or more pharmaceutically acceptable excipients;

a lyophilized formulation comprising about 90 mg of cetrelimab and one or more pharmaceutically acceptable excipients; or
a lyophilized formulation comprising about 240 mg of cetrelimab and one or more pharmaceutically acceptable excipients,
for the treatment of a cancer.

In some embodiments, the lyophilized formulation, once reconstituted, comprises about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

In some embodiments, the drug product is provided for the treatment of a lung cancer, a non-small cell lung cancer (NSCLC), a melanoma, a head and neck cancer, a bladder cancer, a gastrointestinal cancer, a gastric cancer, a gastro-esophageal junction cancer, an esophageal cancer, a liver cancer, a colorectal cancer (CRC), a colon cancer, a gallbladder cancer, a biliary tract cancer, an ovarian cancer, a fallopian tube cancer, a cervical cancer, a peritoneal cancer, an endometrial cancer, a small cell lung cancer (SCLC), a breast cancer, a pancreatic cancer, a renal cell carcinoma, a liver cancer, a Merkel cell carcinoma, a primary mediastinal B-cell lymphoma (PMBCL), a Hodgkin's lymphoma, a non-Hodgkin's lymphoma, a large diffuse B-cell cell lymphoma (DLBLC), a multiple myeloma, a glioblastoma, an urothelial cancer, a salivary cancer, a mesothelioma, an anal cancer, a prostate cancer, a basal cell carcinoma and an advanced cutaneous squamous cell carcinoma (CSCC), or any combination thereof.

In some embodiments, the drug product is provided for the treatment of a NSCLC, a melanoma, a bladder cancer, a renal cell carcinoma, a SLCL, a CRC, a gastric cancer, a prostate cancer, or an esophageal cancer.

In some embodiments, the drug product is provided for the treatment of PD-L1 high NSCLC.

In some embodiments, the drug product is provided for the treatment of a MSI-H CRC or a dMMR CRC.

In some embodiments, the drug product is provided for the treatment of a non-uveal melanoma.

In some embodiments, the drug product is administered
at a dosage of about 240 mg once in two weeks;
at a dosage of about 480 mg once in four weeks; or
as an initial dose of about 240 mg followed by a second dose of about 480 mg six weeks after the initial dose, and thereafter about 480 mg once in four weeks; or

as an initial dose of about 240 mg followed by a second dose of about 480 mg six weeks after the initial dose, and thereafter about 240 mg once in two weeks.

In some embodiments, the drug product the drug product is administered by an intravenous administration of by a subcutaneous administration, or a combination thereof.

Generation of antibodies used in the methods of the invention

Antagonistic anti-PD-1 antibodies or antigen-binding fragments thereof used in the methods of the invention may be generated using various technologies. For example, the hybridoma method of Kohler and Milstein may be used to generate monoclonal antibodies. In the hybridoma method, a mouse or other host animal, such as a hamster, rat or monkey, is immunized with human and/or cyno PD-1 antigens, such as the extracellular domain of PD-1, followed by fusion of spleen cells from immunized animals with myeloma cells using standard methods to form hybridoma cells. Colonies arising from single immortalized hybridoma cells may be screened for production of antibodies with desired properties, such as specificity of binding, cross-reactivity or lack thereof, affinity for the antigen, and functionality such as antagonistic activity.

Exemplary humanization techniques including selection of human acceptor frameworks include CDR grafting (U.S. Patent No. 5,225,539), SDR grafting (U.S. Patent No. 6,818,749), Resurfacing (Padlan, (1991) *Mol Immunol* 28:489-499), Specificity Determining Residues Resurfacing (U.S. Patent Publ. No. 2010/0261620), human framework adaptation (U.S. Patent No. 8,748,356) or superhumanization (U.S. Patent No. 7,709, 226). In these methods, CDRs or a subset of CDR residues of parental antibodies are transferred onto human frameworks that may be selected based on their overall homology to the parental frameworks, based on similarity in CDR length, or canonical structure identity, or a combination thereof.

Humanized antibodies may be further optimized to improve their selectivity or affinity to a desired antigen by incorporating altered framework support residues to preserve binding affinity (backmutations) by techniques such as those described in Int. Patent Publ. Nos. WO1090/007861 and WO1992/22653, or by introducing variation at any of the CDRs for example to improve affinity of the antibody.

Transgenic animals, such as mice or rat carrying human immunoglobulin (Ig) loci in their genome may be used to generate antibodies against PD-1, and are described in for example U.S. Patent No. 6,150,584, Int. Patent Publ. No. WO1999/45962, Int. Patent Publ. Nos. WO2002/066630, WO2002/43478, WO2002/043478 and WO1990/04036. The endogenous immunoglobulin loci in such animal may be disrupted or deleted, and at least one complete or

partial human immunoglobulin locus may be inserted into the genome of the animal using homologous or non-homologous recombination, using transchromosomes, or using minigenes. Companies such as Regeneron (http://_www_regeneron_com), Harbour Antibodies (http://_www_harbourantibodies_com), Open Monoclonal Technology, Inc. (OMT) (http://_www_omtinc_net), KyMab (http://_www_kymab_com), Trianni (http://_www.trianni_com) and Ablexis (http://_www_ablexis_com) may be engaged to provide human antibodies directed against a selected antigen using technologies as described above.

Antibodies may be selected from a phage display library, where the phage is engineered to express human immunoglobulins or portions thereof such as Fabs, single chain antibodies (scFv), or unpaired or paired antibody variable regions. The antibodies of the invention may be isolated for example from phage display library expressing antibody heavy and light chain variable regions as fusion proteins with bacteriophage pIX coat protein as described in Shi *et al.*, (2010) *J Mol Biol* 397:385-96, and Int. Patent Publ. No. WO09/085462). The libraries may be screened for phage binding to human and/or cyno PD-1 and the obtained positive clones may be further characterized, the Fabs isolated from the clone lysates, and expressed as full length IgGs.

The CDRs of an antibody may be grafted on any human framework and the functionality of the resulting antibody may be tested. For example, antibody JNJ-63723283 comprises frameworks derived from human germline genes IGHV1-69 and IGKV3-11. Alternatively, JNJ-63723283 HCDRs may be grafted to other IGHV1 germline gene subgroup frameworks and the LCDRs may be grafted to other IGKV3 germline gene subgroup frameworks and the resulting antibodies are tested for desired functionality. The human germline gene sequences are well known and can be retrieved for example from ImMunoGeneTics Information System®.

Preparation of immunogenic antigens and monoclonal antibody production may be performed using any suitable technique, such as recombinant protein production. The immunogenic antigens may be administered to an animal in the form of purified protein, or protein mixtures including whole cells or cell or tissue extracts, or the antigen may be formed *de novo* in the animal's body from nucleic acids encoding said antigen or a portion thereof.

Methods of producing antibodies

Methods of producing antibodies at large scales are known. Antibodies may be produced for example in CHO cells cultured using known methods. The antibody may be isolated and/or purified from culture medium by removing solids by centrifugation or filtering as a first step in the purification process. The antibody may be further purified by standard methods including chromatography (e.g., ion exchange, affinity, size exclusion, and hydroxyapatite

chromatography), gel filtration, centrifugation, or differential solubility, ethanol precipitation or by any other available technique for the purification of antibodies. Protease inhibitors such as phenyl methyl sulfonyl fluoride (PMSF), leupeptin, pepstatin or aprotinin can be added at any or all stages to reduce or eliminate degradation of the antibody during the purification process. One of ordinary skill in the art will appreciate that the exact purification technique will vary depending on the character of the polypeptide or protein to be purified, the character of the cells from which the polypeptide or protein is expressed, and the composition of the medium in which the cells were grown.

Further embodiments of the invention

Set out below are certain further embodiments of the invention according to the disclosures elsewhere herein. Features from embodiments of the invention set out above described as relating to the invention disclosed herein also relate to each and every one of these further numbered embodiments.

1) An antagonistic anti-PD1 antibody or an antigen binding fragment thereof, comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 for use in treating a subject having a cancer, wherein the antagonistic anti-PD-1 antibody is administered at a dose of between about 240 mg and about 480 mg.
2) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to embodiment 1, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.
3) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to embodiment 1 or 2, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered
    a) at a dosage of about 240 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks;
    b) at the dosage of about 240 mg once every two weeks;
    c) at the dosage of about 240 mg once every three weeks;
    d) at the dosage of about 240 mg once every four weeks;
    e) at the dosage of about 240 mg once every five weeks;

f) at the dosage of about 240 mg once every six weeks;

g) at the dosage of about 480 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks;

h) at the dosage of about 480 mg once every two weeks;

i) at the dosage of about 480 mg once every three weeks;

j) at the dosage of about 480 mg once every four weeks;

k) at the dosage of about 480 mg once every five weeks; or

l) at the dosage of about 480 mg once every six weeks.

4) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to embodiment 1 or 2, wherein the cancer is a solid tumor.

5) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-4, wherein the solid tumor is an advanced solid tumor.

6) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-5, wherein the cancer is selected from the group consisting of a lung cancer, a non-small cell lung cancer (NSCLC), a melanoma, a head and neck cancer, a bladder cancer, a gastrointestinal cancer, a gastric cancer, a gastro-esophageal junction cancer, an esophageal cancer, a liver cancer, a colorectal cancer (CRC), a colon cancer, a gallbladder cancer, a biliary tract cancer, an ovarian cancer, a fallopian tube cancer, a cervical cancer, a peritoneal cancer, an endometrial cancer, a small cell lung cancer (SCLC), a breast cancer, a pancreatic cancer, a renal cell carcinoma, a liver cancer, a Merkel cell carcinoma, a primary mediastinal B-cell lymphoma (PMBCL), a Hodgkin's lymphoma, a non-Hodgkin's lymphoma, a large diffuse B-cell cell lymphoma (DLBLC), a multiple myeloma, a glioblastoma, an urothelial cancer, a salivary cancer, a mesothelioma, an anal cancer, a prostate cancer, a basal cell carcinoma and an advanced cutaneous squamous cell carcinoma (CSCC), or any combination thereof.

7) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-6, wherein the subject is PD-1 axis naïve.

8) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-7, wherein the subject has received one, two, three or more prior therapeutics to treat the cancer.

9) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-8, wherein the one, two, three or more prior therapeutics to treat the cancer are an anti-CTLA4 antibody, ipilimumab, BRAF/MEK inhibitor, chemotherapy or interferon alpha, or any combination thereof.

10) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-9, wherein the subject is resistant, refractory or resistant and refractory to the one, two, three or more prior therapeutics to treat the cancer, or any combination thereof.

11) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-10, wherein the one, two, three or more prior therapeutics to treat the cancer are an anti-CTLA4 antibody, ipilimumab, BRAF/MEK inhibitor, chemotherapy or interferon alpha, or any combination thereof.

12) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-11, wherein the cancer is PD-L1 positive.

13) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-12, wherein the cancer is PD-L1 high.

14) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-13, wherein PD-L1 expression in the cancer is undetermined.

15) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-14, wherein the cancer expresses a mutant BRAF.

16) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-15, wherein the mutant BRAF comprises a V600E mutation.

17) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-16, wherein the cancer expresses a wild-type BRAF.

18) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-17, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is

a) administered or provided for administration in a pharmaceutical composition comprising between about 10 mg/ml to about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

b) administered or provided for administration in a pharmaceutical composition comprising about 10 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

c) administered or provided for administration in a pharmaceutical composition comprising about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment

thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

d) provided for administration as a lyophilized formulation comprising between about 90 mg and about 240 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients;

e) provided for administration as a lyophilized formulation comprising about 90 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients; or

f) provided for administration as a lyophilized formulation comprising about 240 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients.

19) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-18, wherein the lyophilized formulation of d), e) and/or f), once reconstituted, comprises about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

20) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-19, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered by an intravenous infusion.

21) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-20, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered by a subcutaneous injection.

22) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-21, wherein the method achieves an overall response rate (ORR) of at least about 15% in a group of subjects diagnosed with the cancer.

23) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to embodiment 22, wherein the ORR of at least about 15% is achieved after a median duration of treatment of about 1 1/2 months or more.

24) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to embodiment 22 or 23, wherein the method achieves an ORR of at least about 19% in the group of subjects diagnosed with the cancer.

25) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to embodiment 6, wherein the cancer is the non-small cell lung cancer (NSCLC).

26) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to embodiment 25, wherein the method achieves an ORR of at least about 30% in a group of subjects diagnosed with PD-L1 high NSCLC or an ORR of at least about 25% in a group of subjects whose PD-L1 expression in the cancer is undetermined.

27) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to embodiment 25 or 26, wherein the method achieves an ORR of at least about 35% in the group of subjects diagnosed with PD-L1 high NSCLC.

28) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to embodiment 6, wherein the cancer is the melanoma.

29) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to embodiment 28, wherein the method achieves an ORR of at least about 25% in a group of subjects diagnosed with the melanoma.

30) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to embodiment 28 or 29, wherein the melanoma is a non-uveal melanoma.

31) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to embodiment 30, wherein the method achieves an ORR of at least about 30% in a group of subjects diagnosed with the non-uveal melanoma.

32) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to embodiment 31, wherein the CRC is a microsatellite instability-high (MSI-H) CRC or a mismatch repair-deficient (dMMR) CRC, or a combination thereof.

33) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to embodiment 32, wherein the CRC is a stage II CRC or a stage III CRC.

34) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-33, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof comprises a heavy chain variable region (VH) of SEQ ID NO: 7 and a light chain variable region (VL) or SEQ ID NO: 8.

35) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-34, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is an IgG1, an IgG2, an IgG3 or an IgG4 isotype.

36) The antagonistic anti-PD1 antibody or the antigen binding fragment thereof for use according to any one of embodiments 1-35, wherein the antagonistic anti-PD-1 antibody comprises a heavy chain of SEQ ID NO: 9 and a light chain of SEQ ID NO: 10.

37) A pharmaceutical composition comprising

a) between about 10 mg/ml and about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

b) about 10 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

c) about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

d) a lyophilized formulation comprising between about 90 mg and about 240 mg of cetrelimab and one or more pharmaceutically acceptable excipients;

e) a lyophilized formulation comprising about 90 mg cetrelimab and one or more pharmaceutically acceptable excipients; or

f) a lyophilized formulation comprising about 240 mg cetrelimab and one or more pharmaceutically acceptable excipients.

38) The pharmaceutical composition of embodiment 37, wherein the lyophilized formulation of d), e) and/or f), once reconstituted, comprises about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

39) A drug product comprising

a) between about 10 mg/ml and about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

b) about 10 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

c) about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

d) a lyophilized formulation comprising between about 90 mg and about 240 mg cetrelimab and one or more pharmaceutically acceptable excipients;

e) a lyophilized formulation comprising about 90 mg cetrelimab and one or more pharmaceutically acceptable excipients; or

f) a lyophilized formulation comprising about 240 mg cetrelimab and one or more pharmaceutically acceptable excipients.

40) The drug product of embodiment 39, wherein the lyophilized formulation of d), e) and/or f), once reconstituted, comprises about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

41) A drug product comprising

a) between about 10 mg/ml and about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

b) about 10 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

c) about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

d) a lyophilized formulation comprising between about 90 mg and about 240 mg cetrelimab and one or more pharmaceutically acceptable excipients;

e) a lyophilized formulation comprising about 90 mg cetrelimab and one or more pharmaceutically acceptable excipients; or

f) a lyophilized formulation comprising about 240 mg cetrelimab and one or more pharmaceutically acceptable excipients,

for use in treating a subject having a cancer.

42) The drug product of embodiment 41, wherein the lyophilized formulation of d), e) and/or f), once reconstituted, comprises about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

43) The drug product of embodiment 41, wherein the cancer is a lung cancer, a non-small cell lung cancer (NSCLC), a melanoma, a head and neck cancer, a bladder cancer, a gastrointestinal cancer, a gastric cancer, a gastro-esophageal junction cancer, an esophageal cancer, a liver cancer, a colorectal cancer (CRC), a colon cancer, a gallbladder cancer, a biliary tract cancer, an ovarian cancer, a fallopian tube cancer, a cervical cancer, a peritoneal cancer, an endometrial cancer, a small cell lung cancer (SCLC), a breast cancer, a pancreatic cancer, a renal cell carcinoma, a liver cancer, a Merkel cell carcinoma, a primary mediastinal B-cell lymphoma (PMBCL), a Hodgkin's lymphoma, a non-Hodgkin's lymphoma, a large diffuse B-cell cell lymphoma (DLBLC), a multiple myeloma, a glioblastoma, an urothelial cancer, a salivary cancer, a mesothelioma, an anal cancer, a prostate cancer, a basal cell carcinoma and an advanced cutaneous squamous cell carcinoma (CSCC), or any combination thereof.

44) The drug product of embodiment 43, wherein

a) the NSCLC is PD-L1 high NSCLC;

b) the CRC is a MSI-H CRC or a dMMR CRC; or

c) the melanoma is a non-uveal melanoma; or any combination thereof.

45) The drug product of embodiment 41, wherein the drug product is administered

a) at a dosage of about 240 mg once in two weeks;

b) at a dosage of about 480 mg once in four weeks; or

c) as an initial dose of about 240 mg followed by a second dose of about 480 mg six weeks after the initial dose, and thereafter about 480 mg once in four weeks; or

d) as an initial dose of about 240 mg followed by a second dose of about 480 mg six weeks after the initial dose, and thereafter about 240 mg once in two weeks.

46) The drug product of embodiment 41, wherein the drug product is administered by an intravenous administration of by a subcutaneous administration, or a combination thereof.

47) A method of treating a cancer, comprising administering to a subject diagnosed with the cancer an antagonistic anti-PD1 antibody or an antigen binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 at a dosage of between about 80 mg and about 1000 mg once every 2, 3, 4, 5 or 6 weeks.

48) The method of embodiment 47, comprising providing an antagonistic anti-PD1 antibody or an antigen binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 for administration at a dosage of between about 80 mg and about 1000 mg once every 2, 3, 4, 5 or 6 weeks to a subject diagnosed with the cancer, and administering the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof to the subject diagnosed with the cancer.

49) The method of embodiment 48, wherein the cancer is an advanced solid tumor.

50) The method of any one of embodiments 47-49, where the subject has received or is ineligible to receive at least one prior therapeutic to treat the cancer.

51) The method of any one of embodiments 47-50, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at a dosage of about 80 mg, about 160 mg, about 240 mg, about 320 mg, about 400 mg, about 480 mg, about 560 mg, about 720 mg, about 800 mg, about 880 mg or about 960 mg once every 2, 3, 4, 5 or 6 weeks.

52) The method of any one of embodiments 47-51, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered at the dosage of about 240 mg once every 2 weeks or at the dosage of about 480 mg once every 4 weeks.

53) The method of any one of embodiments 47-52, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is provided in a pharmaceutical composition comprising about 10 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM Histidine, about 8.0% (w/v) Sucrose, about 0.04% Polysorbate-20 and about 20 µg/ml and EDTA at pH 6.5.

54) The method of any one of embodiments 47-53, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered by an intravenous infusion.

55) The method of any one of embodiments 47-54, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is diluted into a volume of between about 100 ml and 1000 ml prior to administration.

56) The method of any one of embodiments 47-55, wherein duration of the intravenous infusion is between about 20 minutes and about 80 minutes.

57) The method of any one of embodiments 47-56, wherein duration of the intravenous infusion is about 20, about 30, about 40, about 50, about 60, about 70 or about 80 minutes.

58) The method of any one of embodiments 47-57, wherein the cancer is selected from the group consisting of a thymus cancer, a non-small cell lung cancer (NSCLC), a small cell lung cancer (SCLC), a melanoma, a bladder cancer, a renal cancer, a gastric cancer, an esophageal cancer and a colorectal cancer (CRC).

59) The method of any one of embodiments 47-58, wherein the thymus cancer is a thymoma, a thymic carcinoma or a metastatic thymic cancer, or any combination thereof.

60) The method of any one of embodiments 47-59, wherein the thymoma is a type A thymoma, a type AB thymoma, a type B1 thymoma, a type B2 thymoma or a type B3 thymoma.

61) The method of any one of embodiments 47-60, wherein the thymic carcinoma is a low grade thymic carcinoma or a high grade thymic carcinoma.

62) The method of any one of embodiments 47-61, wherein the thymus cancer has metastasized to lung, lymph node, heart or bone.

63) The method of any one of embodiments 47-62, wherein the subject has been treated with surgery, radiation therapy, a chemotherapy or a hormone therapy.

64) The method of any one of embodiments 47-63, wherein the chemotherapy is carboplatin, cisplatin, cyclophosphamide, doxorubicin, etoposide, ifosfamide, octreotide, paclitaxel or pemetrexed, or any combination thereof.

65) The method of any one of embodiments 47-64, wherein the CRC is a microsatellite instability-high (MSI-H) CRC or a mismatch repair-deficient (dMMR) CRC, or a combination thereof.

66) The method of any one of embodiments 47-65, wherein the CRC is a stage II CRC or a stage III CRC.

67) The method of any one of embodiments 47-66, wherein the subject is refractory to treatment with or has a relapsed CRC after treatment with fluoropyrimidine, oxaliplatin or irinotecan, or any combination thereof.

68) The method of any one of embodiments 47-67, wherein the subject is PD-1 axis naïve.

69) The method of any one of embodiments 47-68, wherein the subject is PD-1 axis naïve and has received at least one prior therapeutic to treat the cancer.

70) The method of any one of embodiments 47-69, wherein the cancer is PD-L1 positive.

71) The method of any one of embodiments 47-70, wherein the cancer is PD-L1 high.

72) The method of any one of embodiments 47-71, wherein the method achieves an overall response rate (ORR) of at least 15% in a group of subjects diagnosed with the cancer.

73) The method of any one of embodiments 47-72, wherein the method achieves an ORR of at least about 35% in a group of subjects diagnosed with MSI-H CRC, an ORR of at least about 35% in a group of subjects diagnosed with dMMR CRC, an ORR of at least about 30% in a group of subjects diagnosed with PD-L1 high NSCLC, or an ORR of at least about 25% in a group of subjects diagnosed with melanoma, or any combination thereof.

74) The method of any one of embodiments 47-73, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof comprises a heavy chain variable region (VH) of SEQ ID NO: 7 and a light chain variable region (VL) or SEQ ID NO: 8.

75) The method of any one of embodiments 47-74, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is an IgG1, an IgG2, and IgG3 or an IgG4 isotype.

76) The method of any one of embodiments 47-75, wherein the antagonistic anti-PD-1 antibody comprises a heavy chain of SEQ ID NO: 9 and a light chain of SEQ ID NO: 10.

77) A pharmaceutical composition comprising about 10 mg/ml of an antagonistic anti-PD-1 antibody comprising a heavy chain (HC) of SEQ ID NO: 9 and a light chain (LC) of SEQ ID NO: 10, about 10 mM Histidine, about 8.0% (w/v) Sucrose, about 0.04% Polysorbate-20 and about 20 µg/ml and EDTA at pH 6.5.

78) A method of treating a thymus cancer, comprising administering to a subject diagnosed with the thymus cancer an antagonistic anti-PD1 antibody or an antigen binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 for a time sufficient to treat the thymus cancer.

79) The method of any embodiment 78, wherein the thymus cancer is a thymoma, a thymic carcinoma or a metastatic thymic cancer, or any combination thereof.

80) The method of any embodiment 78 or 79, wherein the thymoma is a type A thymoma, a type AB thymoma, a type B1 thymoma, a type B2 thymoma or a type B3 thymoma.

81) The method of any one of embodiments 78-80, wherein the thymic carcinoma is a low grade thymic carcinoma or a high grade thymic carcinoma.

82) The method of any one of embodiments 78-81, wherein the thymus cancer has metastasized to lung, lymph node, heart or bone.

83) The method of any one of embodiments 78-82, wherein the subject has been or will be treated with surgery, radiation therapy, a chemotherapy or a hormone therapy, or any combination thereof.

84) The method of any one of embodiments 78-83, wherein the chemotherapy is carboplatin, cisplatin, cyclophosphamide, doxorubicin, etoposide, ifosfamide, octreotide, paclitaxel or pemetrexed, or any combination thereof.

85) The method of any one of embodiments 78-84, wherein the subject is PD-1 axis naïve, has received and/or is ineligible to receive at least one prior therapeutic to treat the cancer, or any combination thereof.

86) The method of any one of embodiments 78-85, wherein the subject is PD-1 axis naïve and has received at least one prior therapeutic to treat the cancer.

87) The method of any one of embodiments 78-86, wherein the cancer is PD-L1 positive.

88) The method of any one of embodiments 78-87, wherein the cancer is PD-L1 high.

89) The method of any one of embodiments 78-88, wherein the method achieves an overall response rate (ORR) of at least 15% in a group of subjects diagnosed with the cancer.

90) The method of any one of embodiments 78-89, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof comprises a heavy chain variable region (VH) of SEQ ID NO: 7 and a light chain variable region (VL) or SEQ ID NO: 8.

91) The method of any one of embodiments 78-90, wherein the antagonistic anti-PD-1 antibody is an IgG1, an IgG2, and IgG3 or an IgG4 isotype.

92) The method of any one of embodiments 78-91, wherein the antagonistic anti-PD-1 antibody comprises a heavy chain of SEQ ID NO: 9 and a light chain of SEQ ID NO: 10.

93) The method of any one of embodiments 78-92, wherein the antagonistic anti-PD1 antibody or the antigen binding fragment thereof is provided in a pharmaceutical composition comprising about 10 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment

thereof, about 10 mM Histidine, about 8.0% (w/v) Sucrose, about 0.04% Polysorbate-20 and about 20 µg/ml and EDTA at pH 6.5.

The present invention will now be described with reference to the following specific, non-limiting examples.

Example 1. A First-in-Human, Open-label, Phase 1/2 Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of JNJ-63723283 (cetrelimab), an Anti-PD-1 Monoclonal Antibody, in Subjects with Advanced Cancers (NCT02908906)

This is a first-in-human (FIH), Phase 1/2, open-label, multicenter study to establish RP2D(s) for JNJ-63723283 in Part 1 and to evaluate the safety and efficacy of the RP2D(s) in Part 2. Part 1 will consist of dosage escalation cohorts and pharmacokinetic/pharmacodynamic cohorts. In Part 2, 1 or more RP2D(s) determined in Part 1 will be evaluated in selected solid tumor types including NSCLC, melanoma, bladder cancer, renal cancer, small-cell lung cancer (SCLC), gastric/esophageal cancer, MSI-H or dMMR CRC, and thymoma (including thymic carcinoma). The overall safety of JNJ-63723283 will be assessed by the Safety Evaluation Team (SET). Subjects will continue to receive JNJ-63723283 until disease progression, unacceptable toxicity, withdrawal of consent, or end of study.

Primary objective:

- To identify the recommended Phase 2 dosage(s) (RP2D[s]) for JNJ-63723283 (Part 1)
- To assess the anti-tumor activity of JNJ-63723283 at the RP2D(s) in subjects with selected advanced cancers including NSCLC, melanoma, renal, bladder, SCLC, gastric/esophageal cancer, high-level microsatellite instability (MSI-H) or mismatch repair-deficient (dMMR) colorectal cancer (CRC), and thymoma (Part 2)

Secondary objectives:

- To characterize the safety of JNJ-63723283 in subjects with advanced solid tumors
- To characterize the pharmacokinetics of JNJ-63723283 administered intravenously
- To assess the immunogenicity of JNJ-63723283
- To assess the clinical activity of JNJ-63723283

Primary endpoint(s)

- Frequency and severity of dosage-limiting toxicity (DLT)
- Overall response rate (ORR) per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in subjects with selected advanced solid tumors

Secondary endpoint(s)

- Safety profile of JNJ-63723283 (safety parameters include but are not limited to the frequency and severity of adverse events [AEs] and immune-related AEs [irAEs], vital signs measurements, clinical laboratory values, and electrocardiograms [ECGs])
- Serum JNJ-63723283 pharmacokinetic parameters including but not limited to maximum observed serum concentration (Cmax), area under the concentration-time curve between 2 defined sampling points, t1 and t2 (AUCt1-t2), half-life (T1/2), total systemic clearance of drug after IV administration (CL), volume of distribution at steady-state (Vss), and accumulation ratio (R)
- Presence of anti-JNJ-63723283 antibodies and effect on serum JNJ-63723283 concentrations
- ORR per the Immune-Related Response Criteria (irRC), duration of response (DOR), clinical benefit rate (CBR), and progression-free survival by both RECIST v.1.1 and irRC, and OS

Exploratory:

- To characterize the pharmacodynamics of JNJ-63723283 including quantification of JNJ-63723283 receptor occupancy on peripheral T cells and cytokine responses to ex vivo stimulation of peripheral T cells
- To explore the relationships between pharmacokinetics, pharmacodynamics, AE profiles, and clinical activity of JNJ-63723283

Subject population

Subjects must be ≥18 years of age and have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. All subjects will have a histologically or cytologically confirmed solid tumor, except lymphoma, that is metastatic or unresectable, and had previously received or were ineligible for standard treatment options. In addition, subjects will not have received prior treatment with an anti-PD-1 or anti-PD-L1 antibody (*i.e.,* anti-PD-1 and anti-PD-L1 naïve). In Part 2, subjects will have one of the following selected tumor types: PD-L1-high NSCLC, bladder, gastric/esophageal, melanoma, renal, SCLC, MSI-H or dMMR CRC.

Dosage and administration

The study drug will initially be administered via IV infusion once every 2 weeks. Dosage escalation will begin at the starting dosage of 80 mg and may continue at dosages 160 mg, 240 mg, 320 mg, 400 mg, 480 mg, 560 mg, 640 mg, 720 mg and 800 mg. The administration schedule and infusion duration may be changed based on emerging safety, pharmacokinetic, and pharmacodynamic/biomarker data, and as confirmed by the SET. In Part 1 alternative dosages and schedules may be explored (*e.g.*, administration once every 3 weeks or every 4 weeks). One or more RP2D(s) for JNJ-63723283 may be evaluated in Part 2.

Safety evaluations

Safety will be assessed by physical examinations, ECOG performance status, clinical laboratory tests, vital signs, electrocardiograms, AE monitoring, and concomitant medication usage. Echocardiogram or multigated acquisition scans will be assessed at screening; subsequent evaluations will be conducted if clinically indicated. The severity of AEs will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4).

Efficacy evaluations

Response to treatment will be assessed by the investigator according to RECIST v1.1 and irRC. Efficacy evaluations will include the following: computed tomography (CT) scans and/or magnetic resonance imaging (MRI), physical examination, and other procedures as necessary.

Statistical methods

The purpose of Part 1 is to identify the RP2D(s) in subjects with advanced solid tumors. Dosage escalation will be supported by a modified Continual Reassessment Method (mCRM) based on a statistical model, Bayesian Logistic Regression Model (BLRM), with Escalation with Overdosage Control (EWOC) principle. The total number of subjects treated will depend on the number of dosage levels explored and the number of subjects enrolled at each dosage level.
In Part 2, it is hypothesized that the ORR of JNJ-63723283 per RECIST v1.1 administered at the RP2D(s) is at least 15% in subjects with selected solid tumors. The following are also hypothesized: 35% ORR for MSI-H/dMMR CRC, 30% ORR for PD-L1-high NSCLC, and 25% ORR for melanoma. The ORR of thymoma is for hypothesis-generating research. Interim monitoring for efficacy will be conducted.

Rationale for Pharmacokinetic and Immunogenicity Sampling

Serum samples will be collected and analyzed in Part 1 and Part 2 for JNJ-63723283 concentrations, and estimation of basic pharmacokinetic parameters from this concentration-time data will be performed. Pharmacokinetics will be assessed relative to available clinical safety, pharmacodynamic, and efficacy data, as well as to any efficacious concentration thresholds observed in nonclinical or competitor studies. Pharmacokinetic or pharmacokinetic/ pharmacodynamic analysis and modeling will be used to aid selection of a RP2D regimen for use in Part 2. Immunogenicity (i.e., ADA) will be evaluated for impact on pharmacokinetics and safety. The serum glycoform profile of JNJ-63723283 will also be characterized.

Rationale for Pharmacodynamic and Biomarker Sampling

It is expected that JNJ-63723283 will induce phenotypic changes consistent with activation of T cells in peripheral blood and tumor tissues. Pharmacodynamic evaluations will be based on assessment of activation and proliferation markers as well as cytokine profiles of T cells in peripheral blood. Peripheral blood samples will also be used to quantify the response of the immune cells in *ex vivo* stimulation assays. As PD-1 polymorphisms could impact the effect of anti-PD-1 antibodies, PD-1 polymorphisms may be evaluated for possible correlation with clinical activity. JNJ-63723283 is anticipated to demonstrate binding to PD-1 on circulating immune cells following administration to human subjects. PD-1 receptor occupancy by JNJ-63723283 on circulating CD3+ T cells will be measured using flow cytometry. Characteristics including dosage-dependence, peak occupancy, plateau occupancy, and duration of occupancy at plateau will be assessed, as feasible.

Rationale for PD-L1 Testing for Part 2

Expression of PD-L1, the ligand for PD-1, correlates with enhanced clinical activity in multiple tumor types including NSCLC cancer. In Part 2, tumor tissue for PD-L1 testing will be required for all tumor types. This is necessary to correlate the clinical response with PD-L1 expression on the tumor tissue.

Rationale for MSI or dMMR Testing for Part 2

Compared with other tumors, MSI-H and dMMR CRC has a higher frequency of DNA mutations and higher level of immune infiltrates, and thus is more susceptible to PD-1 blockade therapies. For the CRC group in Part 2, prescreening for MSI-H or dMMR is required.

DOSING

The recommended FIH starting dosage regimen of JNJ-63723283 is 80 mg administered as an IV infusion every 2 weeks. Additional dosing intervals such as every 3 weeks, 4 weeks, or 6 weeks may be explored in Part 1 in addition to dosing every 2 weeks for further characterization of JNJ-63723283 pharmacology. The maximum administered dosage is planned to be 800 mg but may be lower or higher based on emerging data. Administered intravenously, initially over a 60 (±10) minute infusion. In the absence of infusion-related reactions, subsequent infusions may be administered intravenously over 30 (-5/+10) minutes. Longer infusion times may occur if the infusion needs to be paused or slowed due to a safety concern. Also, it is not recommended to administer ≥100 mL of diluted drug product faster than 30 (-5/+10) minutes, or ≥250 mL of diluted drug product faster than 60 (±10) minutes.

Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. ≥18 years of age
2. Have evaluable disease,

    2a. For Part 2, at least 1 measurable lesion that can be accurately assessed at baseline by CT (or magnetic resonance imaging [MRI] where CT is contraindicated) and is suitable for repeated assessment as per RECIST v1.1

3.2. Type of cancer:

Part 1 of the study:

Has any type of advanced or refractory solid tumor malignancy, except lymphoma, that is metastatic or unresectable and previously received or was ineligible for standard treatment options including appropriate molecularly targeted therapies (e.g., subjects with epidermal growth factor receptor [EGFR] mutant NSCLC or with NSCLC with anaplastic lymphoma tyrosine kinase [ALK] rearrangement).

Part 2 of the study:

Histologically or cytologically confirmed diagnosis of 1 of the following unresectable Stage III or IV solid tumor malignancies and previously received or was ineligible for standard treatment options including appropriate molecularly targeted therapies (e.g., subjects with EGFR mutant NSCLC or with NSCLC with ALK rearrangement):

- NSCLC

- PD-L1-high tumor sample (≥50% tumor cells stained positive for PD-L1) by a PD-L1 immunohistochemistry (IHC) test performed by a local laboratory or by the central laboratory designated by the sponsor
- Documented disease progression on or after at least 1 prior therapy with platinum-containing chemotherapy for advanced/metastatic NSCLC
- Have no more than 3 prior systemic regimens for the treatment of advanced NSCLC and have disease progression on or after last prior treatment (based on RECIST v1.1)

- Bladder cancer (urothelial carcinoma)
- Renal cell carcinoma
- Gastric/esophageal carcinoma
- Melanoma
- SCLC
- MSI-H or dMMR CRC
  - MSI-H or dMMR by a polymerase chain reaction (PCR), next generation sequencing, or IHC test performed by a local laboratory or by the central laboratory designated by the sponsor
  - Progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

4. Have an Eastern Cooperative Oncology Group [ECOG] performance status 0 or 1

5.2. Have organ and bone marrow function as follows without blood product support: Hemoglobin ≥8.5 g/dL, ANC ≥1.5 x 109/L, Platelets ≥75.0 x 109/L, AST and ALT ≤3 x ULN (or ≤4 x ULN for subjects with tumor involvement in the liver), Total bilirubin ≤1.5 x ULNa, Serum creatinine ≤1.5 x ULN or a calculated GFR ≥50 mL/min/1.73mm2, Left ventricular ejection fraction Within normal institutional limits; Corrected QT interval (QTcF or QTcB) ≤480 msec based on the average of triplicate assessments performed 5 (±3) minutes apart

6.1. Has thyroid function laboratory values within normal range. Note: If thyroid stimulating hormone (TSH) is not within normal limits, the subject may still be eligible if T3 (either total or free) and free T4 are within normal limits.

7. Women of childbearing potential must have a negative serum pregnancy test at Screening using highly sensitive pregnancy test.

8. Willing to use contraceptive methods consistent with local regulations for subjects participating in clinical studies during and after the study until 5 months after the last dosage of study drug.

a. Women of childbearing potential must agree to use 2 highly effective methods of contraception consistent with local regulations (<1% per year failure rate when used

consistently and correctly).

b. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control.

c. Women and men must agree not to donate sperm or eggs (ova, oocytes), respectively, during the study and after the study until 5 months after the last dosage of study drug.

9. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

10. Each subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard of care for the subject's disease.

11. Subjects enrolled into Part 2 must have tumor tissue available for correlative studies. Fresh tumor biopsy is preferred. Archival tissue must meet the following criteria: archival sections within 4 months of sectioning that have been stored at 2° to 8° C in the dark or archival tumor blocks within 5 years of collection. Subjects without tissues meeting the aforementioned archived tissue criteria must undergo a fresh biopsy.

Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Has uncontrolled intercurrent illness, including but not limited to ongoing or active infection requiring IV antibiotics, symptomatic congestive heart failure (New York Heart Association class III-IV), unstable angina pectoris, cardiac arrhythmia, poorly controlled hypertension or diabetes, or psychiatric illness/social situation that would limited compliance with study requirements

2. Has had prior treatment with an anti-PD-1 antibody, anti-PD-L1 antibody or anti-PD-L2 antibody

3. Treatment with any local or systemic anti-neoplastic therapy, radiotherapy (excluding limited palliative radiation), or investigational anticancer agent within 14 days or 4 halflives, whichever is longer, up to a maximum wash-out period of 28 days prior to the initiation of study drug administration.

4. Criterion modified per Amendment 2

4.1. Has brain or leptomeningeal metastases unless asymptomatic, have been treated, have been stable for >4 weeks as documented by radiographic imaging with no evidence of cavitation or

hemorrhage in the brain lesion, and do not require prolonged (>2 weeks) systemic corticosteroid therapy. Subjects are not permitted to receive enzyme-inducing antiepileptic drugs.

5. Has not recovered (i.e., ≤Grade 1 or baseline) from AEs except alopecia, peripheral neuropathy related to prior anticancer therapy and stable anemia (i.e., untransfused Hb ≥8.5 g/dL without the need for supportive transfusion within 2 weeks of screening) at the time of treatment allocation

6. Criterion modified per Amendment 2

6.1. Has an active autoimmune disease or a documented history of autoimmune disease that requires systemic steroids or immunosuppressive agents.

Note: Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement will not be excluded from the study. Subjects with a history of transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent (e.g., acute Lyme arthritis) will not be excluded from the study.

7. Grade 3 or higher toxicity effects from previous treatment with immunotherapy

8. Known allergies, hypersensitivity, or intolerance to protein-based therapies or with a history of any significant drug allergy (such as anaphylaxis, hepatotoxicity, or immune-mediated thrombocytopenia or anemia), or to JNJ-63723283 excipients (refer to Investigator's Brochure)

9. Has taken immunosuppressive dosages of systemic medications, such as corticosteroids (dosages

>10 mg/day prednisone or equivalent), within 2 weeks before the planned first dosage of study drug

10. A woman who is pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 5 months after the last dosage of study drug

11. A man who plans to father a child while enrolled in this study or within 5 months after the last dosage of study drug.

12. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

13. Had major surgery (e.g., requiring general anesthesia) within 4 weeks before dosing, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 4 weeks after the last dosage of study drug administration.

Note: Subjects with planned surgical procedures to be conducted under local anesthesia may

participate

14. Criterion modified per Amendment 2

14.1. Active or chronic hepatitis B or hepatitis C disease as determined by hepatitis B surface antigen (HBsAg), hepatitis B core antibody, or hepatitis C antibody (anti-HCV) positivity at screening. If positive, further testing of quantitative levels to rule out active infection is required.

15. Has a history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at Screening

16. Criterion modified per Amendment 2

16.1. Vaccinated with a live vaccine within 28 days prior to the first dosage of study drug. Annual inactivated influenza vaccine is permitted.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dosage of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

Permitted Medications

Throughout the study, investigators may prescribe concomitant medications or treatments (including nutritional support, correction of metabolic disorders, optimal symptom control, and pain management) deemed necessary to provide adequate supportive care. Subjects may continue the use of bisphosphonates or denosumab for bone disease. Concurrent use of hormones for non-cancer related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. Concomitant medications (e.g., acetaminophen/paracetamol or diphenhydramine) deemed necessary by the investigator to provide adequate prophylaxis and management of IRR are allowed.

In addition, the following medications may be administered during the study:

- Standard supportive care therapies (antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor [H2] antagonists or proton pump inhibitors, and other medications intended to treat symptoms or signs of disease) as clinically indicated, according to institutional standards and as deemed necessary by the investigator.
- Documented infectious complication should be treated with oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

- Growth factor support for the management of treatment-emergent hematological toxicity as recommended according to National Comprehensive Cancer Network/European Organization for Research and Treatment of Cancer (NCCN/EORTC) guidelines.

Biomarkers

Tumor Tissue at Baseline

Available (archival or fresh) tumor tissue from consenting subjects will be requested from all subjects in Part 1 and required from all subjects in Part 2 for biomarker analysis of PD-L1 expression by IHC by the sponsor or sponsor's designee. Prescreening PD-L1 testing will be required for NSCLC subjects in Part 2 and may be performed by a local laboratory or by the central laboratory designated by the sponsor. For all CRC subjects, prescreening MSI or dMMR testing will also be required by a local laboratory or by the central laboratory designated by the sponsor. Local test results will be centrally confirmed by the sponsor's designee laboratory. In cases of discordance between local and central results, the central results will be used for analysis. Tumor tissue from the most recent tumor biopsy should be a formalin-fixed paraffin embedded (FFPE) tissue block that has been collected within the past 5 years (preferred) or a minimum of 15 unstained slides that have been processed no more than 4 months prior to study participation and have been stored at 2° C to 8° C in the dark. An additional 5 slides will be collected from CRC patients to support MSI-H analysis. If a site does not have sufficient material, a fresh tumor biopsy will be required for subjects in Part 2. Whole blood will be collected from CRC patients to support tumor tissue MSI and dMMR testing. This blood collection may be stopped due to developments in assay platforms utilized for MSI/dMMR testing.

Physical Description of Study Drug

Drug Product 1 (DP1): The JNJ-63723283 DP1 study material supplied for this study is a sterile, frozen liquid in an 8R glass vial with serum stopper and aluminum seal with flip-off cap. Each vial of JNJ-63723283 clinical study material is filled with 3.3 mL of a 10 mg/mL solution of JNJ-63723283 (including 10% overfill in 10 mM histidine, 8.0% (w/v) sucrose, 0.04% (w/v) polysorbate 20, 20 µg/ml EDTA, pH 6.5, e.g. 30 mg/vial deliverable amount).

Drug Product 2 (DP2): The JNJ-63723283 DP2 study material supplied for this study is a sterile, lyophilized formulation in an 8R glass vial with serum stopper and aluminum seal with flip-off cap. Each vial of JNJ-63723283 clinical study material contains 90 mg per vial that after

reconstitution is a 30 mg/mL solution of JNJ-63723283 in 10 mM histidine, 8.0% (w/v) sucrose, 0.04% Polysorbate 20 (w/v/), 20 µg/ml. EDTA, pH 6.5.

DP3: JNJ-63723283 may also be supplied as a sterile, lyophilized formulation in an 30 mL glass vial with serum stopper and aluminum seal with flip-off cap. Each vial of JNJ-63723283 clinical study material contains 240 mg per vial that after reconstitution is a 30 mg/mL solution of JNJ-63723283 in 10 mM histidine, 8.0% (w/v) sucrose, 0.04% Polysorbate 20 (w/v), 20 µg/ml. EDTA, pH 6.5.

Example 2. Interim results of a phase 1/2 study of JNJ-63723283 in patients with advanced cancers (NCT02908906)

At a clinical data cutoff 11 December 2017, 38 patients were treated with 80 mg, 240 mg, 460 mg or 800 mg of the study drug once every 2 weeks (Q2W), or 480 mg once every 4 weeks (Q4W) in part 1 of the study. Patient demographics and baseline disease characteristics for part 1 are show in **Table 1.** 12 (32%) patients remain on treatment, 26 (68%) have discontinued from study treatment (**Table 2**). Median duration of treatment was 51 days (range 1-297 days).

Table 1.

	Treatment group					
	80 mg	240 mg	460 mg	480 mg	800 mg	Total
Age, years						
Median (range)	49.5	59.0	53.0	56.5	45.5	53.5
Sex, n (%)						
Male	4 (100)	5 (31)	2 (50)	6 (60)	3 (75)	20 (53)
Female	0	11 (69)	2 (50)	4 (40)	1 (25)	18 (47)
Race, n (%)						
White	4 (100)	15 (94)	4 (100)	10 (100)	2 (50)	35 (92)
Black/ African	0	1 (6)	0	0	0	1 (3)
Unknown	0	0	0	0	2 (50)	2 (5)
ECOG PS, n (%)						
0	3 (75)	8 (50)	2 (50)	4 (40)	3 (75)	20 (53)
1	1 (25)	8 (50)	2 (50)	6 (60)	1 (25)	18 (47)
Cancer type, n (%)						
NSCLC	0	3 (19)	1 (25)	0	0	4 (10)
Renal cell	0	0	1 (25)	0	0	1 (3)
SCLC	0	0	0	1 (10)	0	1 (3)

Gastric/Esophageal	0	2 (12)	0	2 (20)	0	4 (10)
Other	4 (100)	11 (69)	2 (50)	7 (70)	4 (100)	28 (74)
Prior lines of therapy, n						
Median (range)	2.5	3.5	2.0	2.0	3.5	3.0

Table 2.

Patients, n (%)	80 mg Q2W (n=4)	240 mg Q2W (n=16)	460 mg Q2W (n=4)	480 mg Q4W (n=10)	800 mg Q2W (n=4)	Total (N=38)
Ongoing treatment	0	4 (25)	1 (25)	4 (40)	3 (75)	12 (32)
Discontinued treatment	4 (100)	12 (75)	3 (75)	6 (60)	1 (25)	26 (68)
Progressive disease	4 (100)	9 (56)	3 (75)	6 (60)	0	22 (58)
Adverse event	0	3 (19)	0	0	0	3 (8)
Death	0	0	0	0	1 (25)	1 (3)

Safety

- Dose Limiting Toxicity (DLT)
  - 240 mg Q2W: Grade 3 pleural effusion in a patient with NSCLC that required pleurodesis on study day 26 that was considered by the investigator to be possibly related to study drug because of the temporal relationship to study drug administration.
  - 800 mg Q2W: Grade 5 dyspnea in a patient with thymoma secondary to myasthenia gravis 14 days after receiving a single dosage of study drug.
- The most common AEs were anemia, fatigue, and vomiting (26% each; **Table 3**); the most common grade 3-4 AEs were pleural effusion, hyponatremia, anemia, and hypertension (8% each).
- Observed serious AEs included pleural effusion (10%) and dyspnea (8%).
  - Immune-related AEs (irAEs) were reported in 37% of patients; most common irAEs were rash, hypothyroidism, and dyspnea (5% each).
  - 3 patients discontinued treatment due to possible/probable grade 3 treatment-related pneumonitis, myopathy, and alanine aminotransferase increased.

Table 3.

Patients, n (%)	80 mg Q2W (n=4)	240 mg Q2W (n=16)	460 mg Q2W (n=4)	480 mg Q4W (n=10)	800 mg Q2W (n=4)	Total (N=38)
Any grade AE	4 (100)	16 (100)	4 (100)	10 (100)	2 (50)	36 (95)
Grade 3-4 AE	2 (50)	9 (56)	2 (50)	6 (60)	0	19 (50)
≥1 serious AE	3 (75)	11 (69)	3 (75)	6 (60)	1 (25)	24 (63)
≥1 irAE	1 (25)	9 (56)	1 (25)	2 (20)	1 (25)	14 (37)
AEs occurring in ≥20% of patients						
Anemia	0	7 (44)	1 (25)	2 (20)	0	10 (26)
Fatigue	0	4 (25)	2 (50)	3 (30)	1 (25)	10 (26)
Vomiting	2 (50)	4 (25)	1 (25)	3 (30)	0	10 (26)
Nausea	0	5 (31)	2 (50)	2 (20)	0	9 (24)
Diarrhea	0	8 (50)	0	0	1 (25)	9 (24)
Hyponatremia	2 (50)	5 (31)	0	1 (10)	0	8 (21)
Hypertension	3 (75)	5 (31)	0	0	0	8 (21)
Decreased appetite	2 (50)	4 (25)	0	2 (20)	0	8 (21)
Sinus tachycardia	2(50)	5 (31)	0	1 (10)	0	8 (21)
AE = adverse event; irAE = immune-related adverse event; Q2W = once every 2 weeks; Q4W = once every 4 weeks						

Preliminary efficacy

4 patients at the 240 mg Q2W dosage (NSCLC, gastric cancer, thymoma, and microsatellite unstable colon cancer) and 1 patient at the 480 mg Q4W dosage (gastric cancer) achieved a partial response (PR). Patient with thymoma had a delayed response 2 months after discontinuation from the study due to immune-mediated hepatitis. 18 (55%) response-evaluable patients achieved stable disease (SD) or better based on RECIST v1.1 (**Table 4** shows the investigator-assessed best overall response.

Table 4.

Patients, n (%)	Treatment group				
	80 mg Q2W	240 mg Q2W	460 mg Q2W	480 mg Q4W	**Total (N=33)**

	(n=4)	(n=16)	(n=4)	(n=9)	
ORR (CR + PR)	0	4 (25)	0	1 (11)	5 (15)
Best overall response					
CR	0	0	0	0	0
PR	0	4 (25)	0	1 (11)	5 (15)
SD	2 (50)	8 (50)	2 (50)	1 (11)	13 (39)
PD	2 (50)	4 (25)	2 (50)	6 (67)	14 (42)
Unknown	0	0	0	1 (11)	1 (3)
ORR = overall response rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; Q2W = once every 2 weeks; Q4W = once every 4 weeks.					

Pharmacokinetics and Receptor Occupancy

Serum concentration of JNJ-63723283 in dosaged subjects were consistent with linear and dosage-proportional PK. **Table 5** shows the preliminary PK parameters of JNJ-63723283 in patients dosaged 80 mg, 240 mg and 480 mg of JNJ-63723283 after the first dosage. **FIG. 1** shows the mean serum concentration -time profiles of JNJ-63723283. Saturation of PD-1 receptors on circulating $CD3^+$ T cells was demonstrated after the first dosage and maintained throughout the dosing interval at all dosage levels (ranging from 80 mg to 480 mg) and all frequencies (ranging from Q2W to Q4W). The percentage (%) saturation of PD-1 receptors on circulating $CD3^+$ T cells is shown in **FIG. 2**. The percentage (%) saturation of PD-1 receptors on circulating $CD3^+$ T cells is shown in **FIG. 3**.

Table 5.

Dosage Level	n	C_{max} (µg/mL) Mean (SD)	T_{max} (hr) Median (range)	C_{min1} (µg/mL) Mean (SD)	AUC_{tau}[c] (µg•hr/mL) Mean (SD)
80 mg Q2W	4	24.6 (3.57)	2.0 (1.0-3.0)	6.08 (0.65)	3591 (156)
240 mg Q2W[a]	10[b]	77.6 (18.4)	1.0 (1.0-3.0)	20.3 (5.2)	11516 (2643)
460 mg Q2W	4	151.2 (7.4)	2.0 (1.0-3.0)	49.9 (1.2)	24637 (4827)
480 mg Q4W[d]	9[e]	171 (49.6)	3.0 (1.0-7.0)	30.1 (13.1)	40493 (14379)
[a] Pooled data from all patients in part 1 receiving 240 mg Q2W.					

[b] n=9 for C_{min1} and AUC_{tau};

[c] tau = 336 hr for the 80, 240, and 460 mg Q2W dosage groups; tau = 672 hr for the 480 mg Q4W dosage group.

[d] Pooled data from all patients in part 1 receiving 480 mg Q4W.

[e] n=8 for C_{min1} and AUC_{tau}.

AUC_{tau} = area under the curve for 1 dosing interval; C_{max} = maximum serum concentration; C_{min1} = minimum serum concentration after the first dosage; PK = pharmacokinetics; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SD = standard deviation; T_{max} = time to maximum serum concentration.

T cell functionality in treated patients

PBMCs from treated patients showed near maximal T cell activation in an ex vivo SEB stimulation assay at all dosages and time points tested. **FIG. 4** shows the T cell activation in response to SEB prior to and 2 hours after dosage 1 (D1-Pre, D1-2hr), at follow-up after dosage 1 (D1-FU), prior to dosage 2 (D2-Pre), prior to dosage 3 (D3-Pre) and at end of treatment (EOT) in patients who received 240 mg Q2W or 480 mg Q4Q of the antibody.

Methods: JNJ-63723283 pharmacodynamic modulation was characterized by evaluating IL-2 expression, as a measure of T cell activation, in pre-and post-treated *ex vivo* SEB (Staphylococcal enterotoxin B) stimulated whole blood samples. Briefly, blood samples were diluted 1:10 with RPMI 1640 media followed by a 4-day incubation with 100ng/ml of SEB plus 10 μg/ml of JNJ-63723283 or isotype control, representing maximum and endogenous levels of IL-2 expression, respectively. The ratio of IL-2 expression levels between the isotype and JNJ-63723283 *ex vivo* treated blood samples was then calculated to assess the degree of PD modulation, with a ratio of 1 indicating maximum T cell activation.

Conclusions

- JNJ-63723283 displayed a safety profile that was comparable to other anti-PD-1 antibodies.
- The RP2D of 240 mg Q2W is being evaluated in phase 2; the RP2D may be administered at an alternative regimen of 480 mg Q4W to enable flexibility in various clinical settings.
- Preliminary antitumor activity in patients with previously treated advanced cancers was observed, with 5 patients (15%) achieving a PR and 13 patients (39%) achieving SD.
- JNJ-63723283 exhibited linear and dose-proportional PK within the dose range evaluated.

• JNJ-63723283 demonstrated saturable PD-1 RO and enhanced T cell activity in *ex-vivo* SEB stimulation assays at all dose levels and throughout all dosing frequencies tested.

• Additional dose levels and dosing frequencies may be explored.

• The trial is ongoing to further characterize the safety, PK, and clinical activity of JNJ-63723283.

Example 3. Interim results of a phase 1/2 study of JNJ-63723283 in patients with advanced cancers (NCT02908906)

At a clinical data cutoff 04 December 2018, 198 patients were treated with 80 mg, 240 mg, 460 mg or 800 mg of the study drug DP1 once every 2 weeks (Q2W), or 480 mg of the study drug DP1 or DP2 once every 4 weeks (Q4W) in part 1/2 of the study. Patient demographics and baseline disease characteristics for part 1 and part 2 subjects are shown in **Table 6.**

Table 6.

Total Number of Subjects	NSCLC	Melanoma	Bladder	Renal Cell	SCLC	MSI-H/ dMMR	Gastric/ Esophageal	Other	Total
(N)	35	50	4	2	11	47	16	33	198
Sex (M:F)	29:6	29:21	3:1	1:1	7:4	20:27	10:6	15:18	114: 84
ECOG									
0	13	29	2	0	3	26	8	18	99
1	22	21	2	2	8	21	8	15	99
No. Prior Regimens									
0	0	13	0	0	0	0	0	0	13
1	18	12	1	1	5	2	3	5	47
2	12	15	2	0	4	20	6	8	67
≥3	5	10	1	1	2	25	7	20	71
Grade at Screening									

Well Diff	3	0	0	0	0	1	0	2	3
Mod Diff	2	0	0	0	0	15	1	2	18
Poorly Diff	5	0	2	1	1	10	3	1	18
Other	0	2	0	0	0	2	2	1	7
N/A	0	15	0	0	0	0	1	2	18
Unknown	25	33	2	1	10	19	9	25	99
Stage at Screening									
II								1	1
III	2	1			1				4
IV	33	42	4	2	10	43	15	26	142
IVA		2				0	1	3	6
IVB		5				4	0	3	12
PDL1									
Positive	19	12							31
Negative	12	31							43
Unknown	4	7							11
Ongoing Treatment	15	22	0	1	1	22	1	5	67
Discontinued Treatment	20	28	4	1	10	25	15	28	131
Treatment Duration Median (days)	127	198	55	303	51	85	56.5	71	103
Reason for Discontinuation									
AE	2	3	0	0	0	5	0	2	12
Death	0	0	0	0	0	1	2	1	4
WD by Subject	0	0	0	0	0	1	0	1	2

PD	17	25	4	1	10	17	12	24	110
Other	1	0	0	0	0	1	1	0	3

Table 7 shows the mutation status, number and type of prior therapies for melanoma patients in Part 2. **Table 8** shows the PD-L1 status, number and type of prior therapies for NSCLC patients in Part 2. **Table 9** shows the MSI (Microsatellite Instability) status (Central testing result) in CRC.

Table 7.

Mutation status	
BRAF Mutation V600E: N (%)	20 (46.5%)
BRAF Wildtype: N (%)	18 (41.9%)
Number of Prior Therapies	
0	13 (26.0%)
1	12 (24.0%)
2	15 (30.0%)
≥3	10 (20.0%)
Type of Prior Therapies	
Ipilimumab: N (%)	19 (38%)
BRAF/MEK: N (%)	13 (26%)
Chemotherapy: N (%)	18 (36%)
Interferon alpha: N (%)	12 (24%)

Table 8.

PDL1 status	**Number of patients (percentage of patients)***
Positive	19 (63.3%)
Negative	11 (36.7%)
Number of Prior Therapies	
0	0
1	16 (53.3%)

2	11 (36.7%)
≥3	3 (10.0%)
Type of Prior Therapies	
Ipilimumab: N (%)	0
BRAF/MEK: N (%)	0
Chemotherapy: N (%)	29 (96.7%)
Interferon alpha: N (%)	0
*percentages expressed as percent of NSCLC patients enrolled into Part 2	

Table 9.

MSI Status (Central testing)	**Number of patients (percentage of patients)***
Abnormal (High)	19 (45.2%)
Normal	12 (28.6%)
Other	11 (26.2%)
*Percentages expressed as percent of locally confirmed MSI-High/dMMR CRC patients enrolled into Part 2.	

Safety

- The most common TE-AEs (Treatment Emergent Adverse Events) reported were asthenia (22.2%), fatigue (19.2%), diarrhea (18.2%), dyspnoea (18.2%), pyrexia (17.7%), decreased appetite (16.7%), anaemia (16.7%), nausea (15.7%), back pain (14.1%), ALT increased (12.6%), cough (12.1%), vomiting (11.6%), AST increased (11.6%), abdominal pain (10.1%), constipation (10.1%).
- The most common grade 3-4 TE-AEs reported were anaemia (6.6%), dyspnea (5.1%), pleural effusion (2.5%), pyrexia (5.1%), hyponatremia (3.0%), hyperamylasemia (2.5%), abdominal pain (2.5%), intestinal obstruction (2.5%), fatigue (2.5%), general physical health deterioration (2.5%), ALT increased (3.0%), AST increased (3.0%), GGT increased (3.0%), and hypertension (3.0%).
- Serious TEAEs were observed in nearly 50% of subjects. The most common TE SAEs were dyspnoea (5.1%), pleural effusion (3.5%), intestinal obstruction (3.5%), general physical health deterioration (3.0%), and pyrexia (3.0%).
- Immune-related AEs (irAEs) were reported in 35.9% of patients.

- Infusion Related Reactions (IRRs) were reported in 14.1% of all subjects, and 13.6% in subjects receiving the 240 mg Q2W dose. All except 2 IRRs were CTCAE grade 1/2. Only 1 subject did not complete an infusion due to an IRR of a grade 3 hypertension event.

Table 10 shows the summary of the reported adverse events in part 1/2. **Table 11** shows the adverse events occurring in >10% subjects.

Table 10.

	80 mg Q2W	240 mg Q2W	460 mg Q2W	480 mg Q4W		800 mg Q2W	Total
				DP1	DP2		
Number of Subjects	4	162	4	11	11	6	198
All TE-AEs	4 (100.0%)	150 (92.6%)	4 (100.0%)	11 (100.0%)	10 (90.9%)	6 (100.0%)	185 (93.4%)
Grade 3 or higher TE-AEs	2 (50.0%)	79 (48.8%)	2 (50.0%)	7 (63.6%)	5 (45.5%)	5 (83.3%)	100 (50.5%)
SAEs	3 (75.0%)	73 (45.1%)	3 (75.0%)	6 (54.5%)	4 (36.4%)	5 (83.3%)	94 (47.5%)
Fatal TE-AEs	0	0	0	0	0	1 (16.7%)	1 (0.5%)
irAEs	1 (25.0%)	64 (39.5%)	1 (25.0%)	1 (9.1%)	2 (18.2%)	2 (33.3%)	71 (35.9%)
Grade 3 or higher irAEs	0	11 (6.8%)	0	0	0	2 (33.3%)	13 (6.6%)
IRR	0	22 (13.6%)	1 (25.0%)	1 (9.1%)	1 (9.1%)	3 (50.0%)	28 (14.1%)
Grade 3 or higher IRRs	0	1 (0.6%)	0	0	0	1 (16.7%)	2 (1.0%)

TE-AE: treatment emergent adverse events
SAE: serious adverse events
irAE: immune related TE-AEs
IRR: infusion related reactions

Table 11.

	80 mg N=4	240 mg N=162	460 mg N=4	480 mg Q4W		800 mg N=6	Total N=198
				DP1, N=11	DP2, N=11		

Subject with TEAEs	4 (100.0%)	150 (92.6%)	4 (100.0%)	11 (100.0%)	10 (90.9%)	6 (100.0%)	185 (93.4%)
Preferred Term*							
Asthenia	0	40 (24.7%)	1 (25.0%)	2 (18.2%)	0	1 (16.7%)	44 (22.2%)
Fatigue	0	27 (16.7%)	2 (50.0%)	4 (36.4%)	2 (18.2%)	3 (50.0%)	38 (19.2%)
Diarrhoea	0	32 (19.8%)	0	0	2 (18.2%)	2 (33.3%)	36 (18.2%)
Dyspnoea	1 (25.0%)	31 (19.1%)	0	2 (18.2%)	1 (9.1%)	1 (16.7%)	36 (18.2%)
Pyrexia	0	31 (19.1%)	0	2 (18.2%)	1 (9.1%)	1 (16.7%)	35 (17.7%)
Decreased appetite	2 (50.0%)	27 (16.7%)	0	2 (18.2%)	2 (18.2%)	0	33 (16.7%)
Anaemia	0	26 (16.0%)	1 (25.0%)	3 (27.3%)	1 (9.1%)	2 (33.3%)	33 (16.7%)
Nausea	0	25 (15.4%)	2 (50.0%)	2 (18.2%)	1 (9.1%)	1 (16.7%)	31 (15.7%)
Back pain	0	22 (13.6%)	0	3 (27.3%)	2 (18.2%)	1 (16.7%)	28 (14.1%)
Alanine aminotransferase increased	1 (25.0%)	22 (13.6%)	0	0	1 (9.1%)	1 (16.7%)	25 (12.6%)
Cough	1 (25.0%)	22 (13.6%)	0	0	1 (9.1%)	0	24 (12.1%)
Vomiting	2 (50.0%)	15 (9.3%)	1 (25.0%)	3 (27.3%)	1 (9.1%)	1 (16.7%)	23 (11.6%)
Aspartate aminotransferase increased	1 (25.0%)	19 (11.7%)	0	1 (9.1%)	1 (9.1%)	1 (16.7%)	23 (11.6%)
Abdominal pain	1 (25.0%)	14 (8.6%)	0	3 (27.3%)	0	2 (33.3%)	20 (10.1%)

Constipation	0	11 (6.8%)	2 (50.0%)	3 (27.3%)	4 (36.4%)	0	20 (10.1%)
*Occurring in >10% subjects, All treated subjects (N=198)							
TEAE: Treatment Emergent Adverse Event							

Preliminary efficacy observed in Part 2 subjects.

140 patients at the 240 mg Q2W dosage (NSCLC, melanoma, and MSI-H/dMMR CRC) were evaluable for response evaluation based on 04 Dec 2018 dataset. 4 (2.9%) patients achieved a complete response (CR) and 23 (16.4%) achieved a partial response (PR). 73 (52.1%) response-evaluable patients achieved stable disease (SD) or better based on RECIST v1.1. The following ORRs were observed by histologic subtype: 37.5% in PDL1+ $\geq$ 50% NSCLC, 32.6% in non-uveal melanoma, and 12.5% in MSI-H/dMMR CRC. In patients with centrally confirmed MSI-H CRC, the ORR increased to 16.7%. (**Table 12** shows the investigator-assessed best overall response and associated 80% confidence intervals.)

Table 12.

	Treatment Group					
	NSCLC (Unselected)	NSCLC (PDL1+ $\geq$ 50%)	Melanoma	Melanoma (excluding Uveal)	CRC	All Part 2
N	27	16	49	43	40	140
ORR: N (%) 80% CI	7 (25.9%) (15.1- 39.7)	6 (37.5%) (21.0-56.5)	14 (28.6%) (20.1-38.4)	14 (32.6%) (23.1-43.4)	5 (12.5%) (6.2-22.0)	27 (19.3%)
Confirmed ORR 80% CI	5 (18.5%) (9.3-31.7)	4 (25%) (11.4-43.9)	13 (26.5%) (18.3-36.3)	13 (30.2%) (21.0-40.9)	3 (7.5%) (2.8-15.9)	22 (15.7%)

DCR (CR+PR+SD) 80% CI	18 (66.7%) (52.5-78.8)		32 (65.3%) (55.2-74.4)	32 (74.4%)	19 (47.5%) (36.4-58.8)	73 (52.1%)
Best Response						
CR	0		4 (8.2%)	4 (9.3%)	0 (0%)	4 (2.9%)
PR	7 (25.9%)		10 (20.4%)	10 (23.3%)	5 (12.5%)	23 (16.4%)
SD	11 (40.7%)		18 (36.7%)	18 (41.9%)	14 (35.0%)	46 (32.9%)
PD	9 (33.3%)		17 (34.7%)	11 (25.6%)	21 (52.5%)	67 (47.9%)
ORR = overall response rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; CI = Confidence Interval						

Conclusions

• JNJ-63723283 displayed a safety profile in immune-sensitive advanced cancers that was comparable to other anti-PD-1 antibodies.

• JNJ-63723283 exhibited linear and dose-proportional PK within the dose range evaluated.

• JNJ-63723283 demonstrated saturable PD-1 RO and enhanced T cell activity in *ex-vivo* SEB stimulation assays at all dose levels and throughout all dosing frequencies tested.

• The RP2D of 240 mg Q2W is being evaluated in phase 2; the RP2D may be administered at an alternative regimen of 480 mg Q4W to enable flexibility in various clinical settings.

  • Additional dose levels, administration routes (subcutaneous injection), and dosing frequencies may be explored.

• Patients with advanced cancers achieved an ORR of 19% overall; by histologic subtype, observed ORRs were 37.5% in PDL1+ NSCLC, 32.6% in non-uveal melanoma, and 13% in MSI-H/dMMR.

  • Follow-up is ongoing on the centrally confirmed MSI-H CRC cohort

• The trial is ongoing to further characterize the safety, PK, and clinical activity of JNJ-63723283 at the RP2D of 240 mg Q2W.

We claim:

1) A method of treating a cancer, comprising administering to a subject diagnosed with the cancer an antagonistic anti-PD1 antibody or an antigen binding fragment thereof, comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6 at a dose of between about 240 mg and about 480 mg.
2) The method of claim 1, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.
3) The method of claim 2, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered
    a) at a dosage of about 240 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks;
    b) at the dosage of about 240 mg once every two weeks;
    c) at the dosage of about 240 mg once every three weeks;
    d) at the dosage of about 240 mg once every four weeks;
    e) at the dosage of about 240 mg once every five weeks;
    f) at the dosage of about 240 mg once every six weeks;
    g) at the dosage of about 480 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks;
    h) at the dosage of about 480 mg once every two weeks;
    i) at the dosage of about 480 mg once every three weeks;
    j) at the dosage of about 480 mg once every four weeks;
    k) at the dosage of about 480 mg once every five weeks; or
    l) at the dosage of about 480 mg once every six weeks.
4) The method of claim 3, wherein the cancer is a solid tumor.
5) The method of claim 4, wherein the solid tumor is an advanced solid tumor.
6) The method of claim 3, wherein the cancer is selected from the group consisting of a lung cancer, a non-small cell lung cancer (NSCLC), a melanoma, a head and neck cancer, a bladder cancer, a gastrointestinal cancer, a gastric cancer, a gastro-esophageal junction cancer, an esophageal cancer, a liver cancer, a colorectal cancer (CRC), a colon cancer, a gallbladder cancer, a biliary tract cancer, an ovarian cancer, a fallopian tube cancer, a cervical cancer, a peritoneal cancer, an endometrial cancer, a small cell lung cancer (SCLC), a breast

cancer, a pancreatic cancer, a renal cell carcinoma, a liver cancer, a Merkel cell carcinoma, a primary mediastinal B-cell lymphoma (PMBCL), a Hodgkin's lymphoma, a non-Hodgkin's lymphoma, a large diffuse B-cell cell lymphoma (DLBLC), a multiple myeloma, a glioblastoma, an urothelial cancer, a salivary cancer, a mesothelioma, an anal cancer, a prostate cancer, a basal cell carcinoma and an advanced cutaneous squamous cell carcinoma (CSCC), or any combination thereof.

7) The method of claim 6, wherein the subject is PD-1 axis naïve.
8) The method of claim 6, wherein the subject has received one, two, three or more prior therapeutics to treat the cancer.
9) The method of claim 8, wherein the one, two, three or more prior therapeutics to treat the cancer are an anti-CTLA4 antibody, ipilimumab, BRAF/MEK inhibitor, chemotherapy or interferon alpha, or any combination thereof.
10) The method of claim 8, wherein the subject is resistant, refractory or resistant and refractory to the one, two, three or more prior therapeutics to treat the cancer, or any combination thereof.
11) The method of claim 10, wherein the one, two, three or more prior therapeutics to treat the cancer are an anti-CTLA4 antibody, ipilimumab, BRAF/MEK inhibitor, chemotherapy or interferon alpha, or any combination thereof.
12) The method of claim 6, wherein the cancer is PD-L1 positive.
13) The method of claim 12, wherein the cancer is PD-L1 high.
14) The method of claim 6, wherein PD-L1 expression in the cancer is undetermined.
15) The method of claim 6, wherein the cancer expresses a mutant BRAF.
16) The method of claim 15, wherein the mutant BRAF comprises a V600E mutation.
17) The method of claim 6, wherein the cancer expresses a wild-type BRAF.
18) The method of claim 6, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is
    a) administered or provided for administration in a pharmaceutical composition comprising between about 10 mg/ml to about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
    b) administered or provided for administration in a pharmaceutical composition comprising about 10 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

c) administered or provided for administration in a pharmaceutical composition comprising about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

d) provided for administration as a lyophilized formulation comprising between about 90 mg and about 240 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients;

e) provided for administration as a lyophilized formulation comprising about 90 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients; or

f) provided for administration as a lyophilized formulation comprising about 240 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients.

19) The method of claim 18, wherein the lyophilized formulation of d), e) and/or f), once reconstituted, comprises about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

20) The method of claim 6, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered by an intravenous infusion.

21) The method of claim 6, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is administered by a subcutaneous injection.

22) The method of claim 6, wherein the method achieves an overall response rate (ORR) of at least about 15% in a group of subjects diagnosed with the cancer.

23) The method of claim 22, wherein the ORR of at least about 15% is achieved after a median duration of treatment of about 1 1/2 months or more.

24) The method of claim 22, wherein the method achieves an ORR of at least about 19% in the group of subjects diagnosed with the cancer.

25) The method of claim 6, wherein the cancer is the non-small cell lung cancer (NSCLC).

26) The method of claim 25, wherein the method achieves an ORR of at least about 30% in a group of subjects diagnosed with PD-L1 high NSCLC or an ORR of at least about 25% in a group of subjects whose PD-L1 expression in the cancer is undetermined.

27) The method of claim 26, wherein the method achieves an ORR of at least about 35% in the group of subjects diagnosed with PD-L1 high NSCLC.

28) The method of claim 6, wherein the cancer is the melanoma.

29) The method of claim 28, wherein the method achieves an ORR of at least about 25% in a group of subjects diagnosed with the melanoma.

30) The method of claim 29, wherein the melanoma is a non-uveal melanoma.

31) The method of claim 30, wherein the method achieves an ORR of at least about 30% in a group of subjects diagnosed with the non-uveal melanoma.

32) The method of claim 6, wherein the CRC is a microsatellite instability-high (MSI-H) CRC or a mismatch repair-deficient (dMMR) CRC, or a combination thereof.

33) The method of claim 32, wherein the CRC is a stage II CRC or a stage III CRC.

34) The method of claim 6, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof comprises a heavy chain variable region (VH) of SEQ ID NO: 7 and a light chain variable region (VL) or SEQ ID NO: 8.

35) The method of claim 34, wherein the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is an IgG1, an IgG2, an IgG3 or an IgG4 isotype.

36) The method of claim 35, wherein the antagonistic anti-PD-1 antibody comprises a heavy chain of SEQ ID NO: 9 and a light chain of SEQ ID NO: 10.

37) A pharmaceutical composition comprising

a) between about 10 mg/ml and about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

b) about 10 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

c) about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;

d) a lyophilized formulation comprising between about 90 mg and about 240 mg of cetrelimab and one or more pharmaceutically acceptable excipients;

e) a lyophilized formulation comprising about 90 mg cetrelimab and one or more pharmaceutically acceptable excipients; or

f) a lyophilized formulation comprising about 240 mg cetrelimab and one or more pharmaceutically acceptable excipients.

38) The pharmaceutical composition of claim 37, wherein the lyophilized formulation of d), e) and/or f), once reconstituted, comprises about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

39) A drug product comprising

a) between about 10 mg/ml and about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
b) about 10 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
c) about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
d) a lyophilized formulation comprising between about 90 mg and about 240 mg cetrelimab and one or more pharmaceutically acceptable excipients;
e) a lyophilized formulation comprising about 90 mg cetrelimab and one or more pharmaceutically acceptable excipients; or
f) a lyophilized formulation comprising about 240 mg cetrelimab and one or more pharmaceutically acceptable excipients.

40) The drug product of claim 39, wherein the lyophilized formulation of d), e) and/or f), once reconstituted, comprises about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

41) A drug product comprising
a) between about 10 mg/ml and about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
b) about 10 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
c) about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5;
d) a lyophilized formulation comprising between about 90 mg and about 240 mg cetrelimab and one or more pharmaceutically acceptable excipients;
e) a lyophilized formulation comprising about 90 mg cetrelimab and one or more pharmaceutically acceptable excipients; or
f) a lyophilized formulation comprising about 240 mg cetrelimab and one or more pharmaceutically acceptable excipients,
for the treatment of a cancer.

42) The drug product of claim 41, wherein the lyophilized formulation of d), e) and/or f), once reconstituted, comprises about 30 mg/ml cetrelimab, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 µg/ml EDTA at pH 6.5.

43) The drug product of claim 41, wherein the cancer is a lung cancer, a non-small cell lung cancer (NSCLC), a melanoma, a head and neck cancer, a bladder cancer, a gastrointestinal cancer, a gastric cancer, a gastro-esophageal junction cancer, an esophageal cancer, a liver cancer, a colorectal cancer (CRC), a colon cancer, a gallbladder cancer, a biliary tract cancer, an ovarian cancer, a fallopian tube cancer, a cervical cancer, a peritoneal cancer, an endometrial cancer, a small cell lung cancer (SCLC), a breast cancer, a pancreatic cancer, a renal cell carcinoma, a liver cancer, a Merkel cell carcinoma, a primary mediastinal B-cell lymphoma (PMBCL), a Hodgkin's lymphoma, a non-Hodgkin's lymphoma, a large diffuse B-cell cell lymphoma (DLBLC), a multiple myeloma, a glioblastoma, an urothelial cancer, a salivary cancer, a mesothelioma, an anal cancer, a prostate cancer, a basal cell carcinoma and an advanced cutaneous squamous cell carcinoma (CSCC), or any combination thereof.

44) The drug product of claim 43, wherein

a) the NSCLC is PD-L1 high NSCLC;

b) the CRC is a MSI-H CRC or a dMMR CRC; or

c) the melanoma is a non-uveal melanoma; or any combination thereof.

45) The drug product of claim 41, wherein the drug product is administered

a) at a dosage of about 240 mg once in two weeks;

b) at a dosage of about 480 mg once in four weeks; or

c) as an initial dose of about 240 mg followed by a second dose of about 480 mg six weeks after the initial dose, and thereafter about 480 mg once in four weeks; or

d) as an initial dose of about 240 mg followed by a second dose of about 480 mg six weeks after the initial dose, and thereafter about 240 mg once in two weeks.

46) The drug product of claim 41, wherein the drug product is administered by an intravenous administration of by a subcutaneous administration, or a combination thereof.

FIG. 1

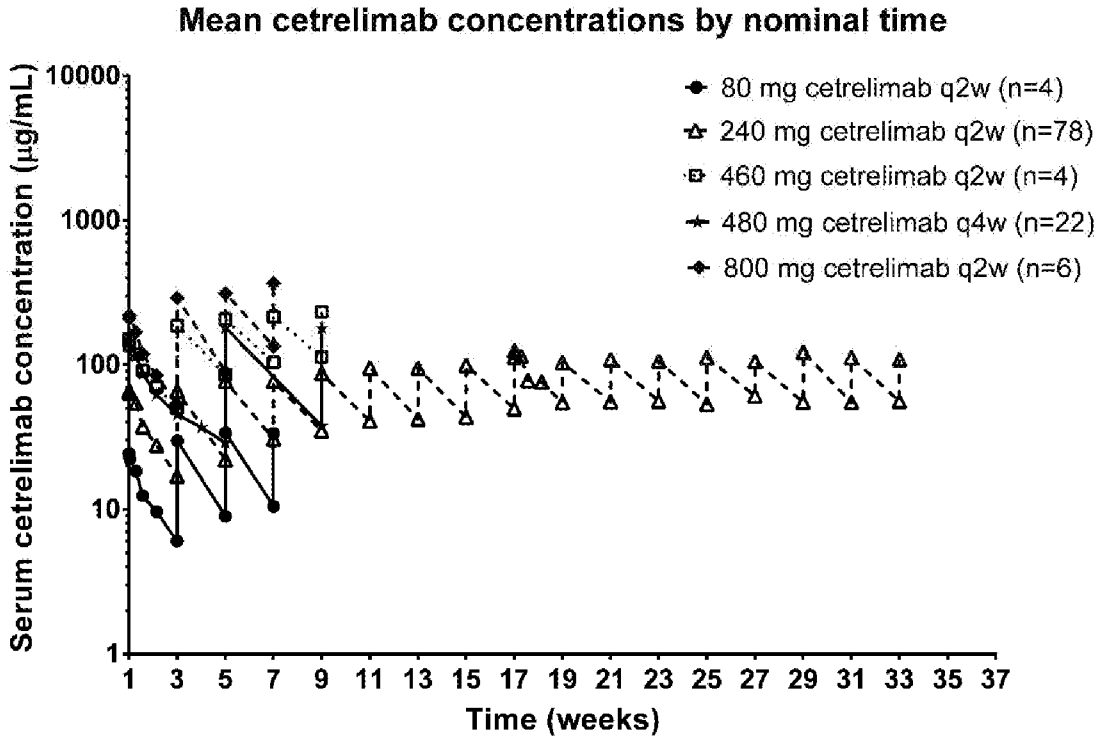

Mean cetrelimab concentrations by nominal time
Serum cetrelimab concentration (µg/mL)
10000
1000
100
10
1
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37
Time (weeks)
80 mg cetrelimab q2w (n=4)
240 mg cetrelimab q2w (n=78)
460 mg cetrelimab q2w (n=4)
480 mg cetrelimab q4w (n=22)
800 mg cetrelimab q2w (n=6)

FIG. 2

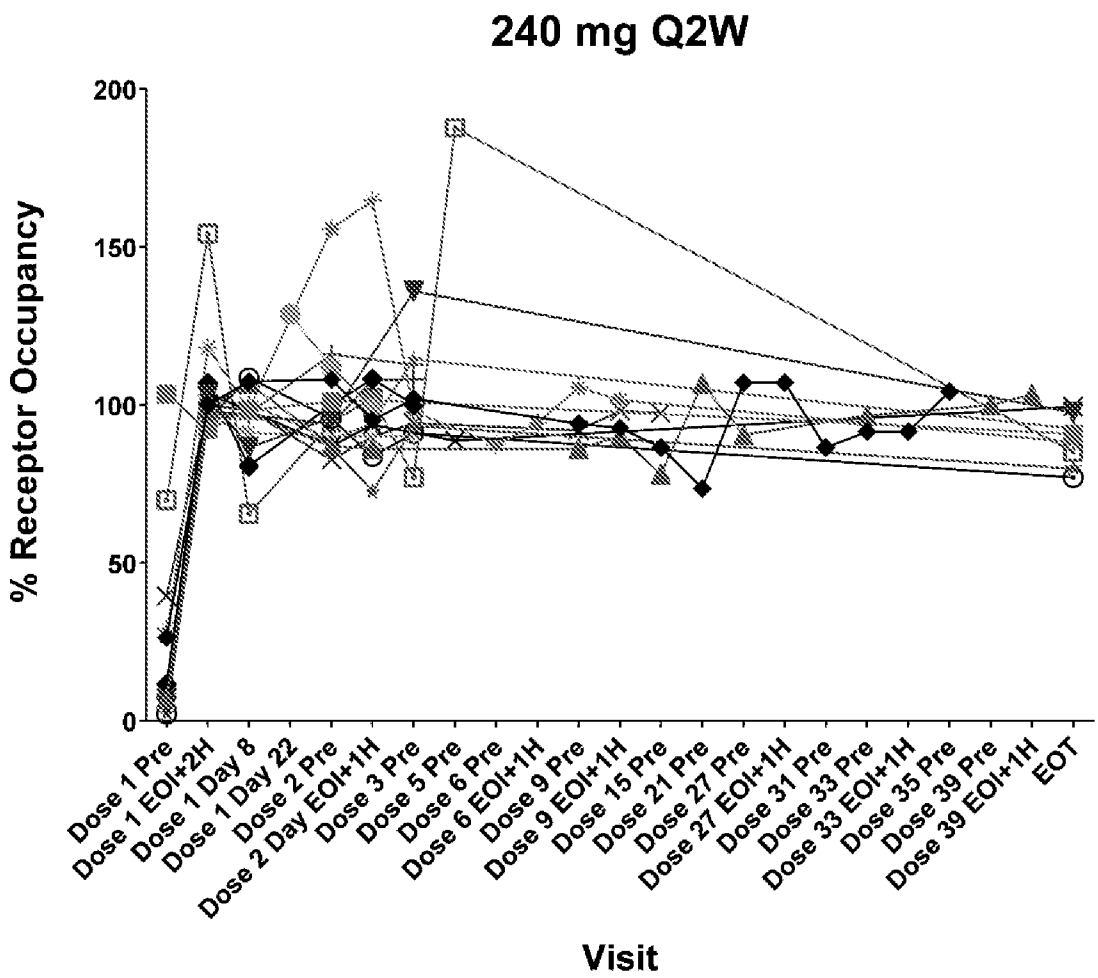

240 mg Q2W
% Receptor Occupancy
200
150
100
50
0
Dose 1 Pre
Dose 1 EOI+2H
Dose 1 Day 8
Dose 1 Day 22
Dose 2 Pre
Dose 2 Day EOI+1H
Dose 3 Pre
Dose 5 Pre
Dose 6 Pre
Dose 6 EOI+1H
Dose 9 Pre
Dose 9 EOI+1H
Dose 15 Pre
Dose 21 Pre
Dose 27 Pre
Dose 27 EOI+1H
Dose 31 Pre
Dose 33 Pre
Dose 33 EOI+1H
Dose 35 Pre
Dose 39 Pre
Dose 39 EOI+1H
EOT
Visit

FIG. 3

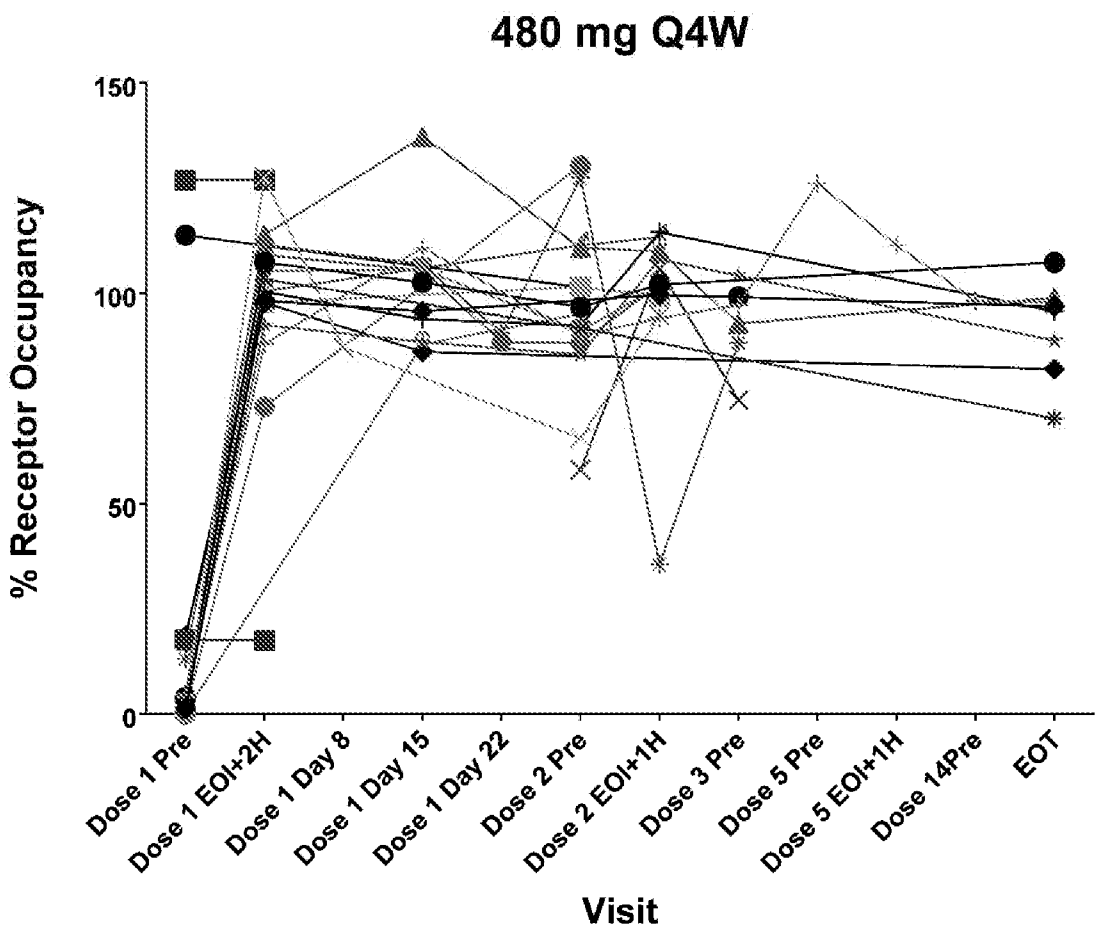
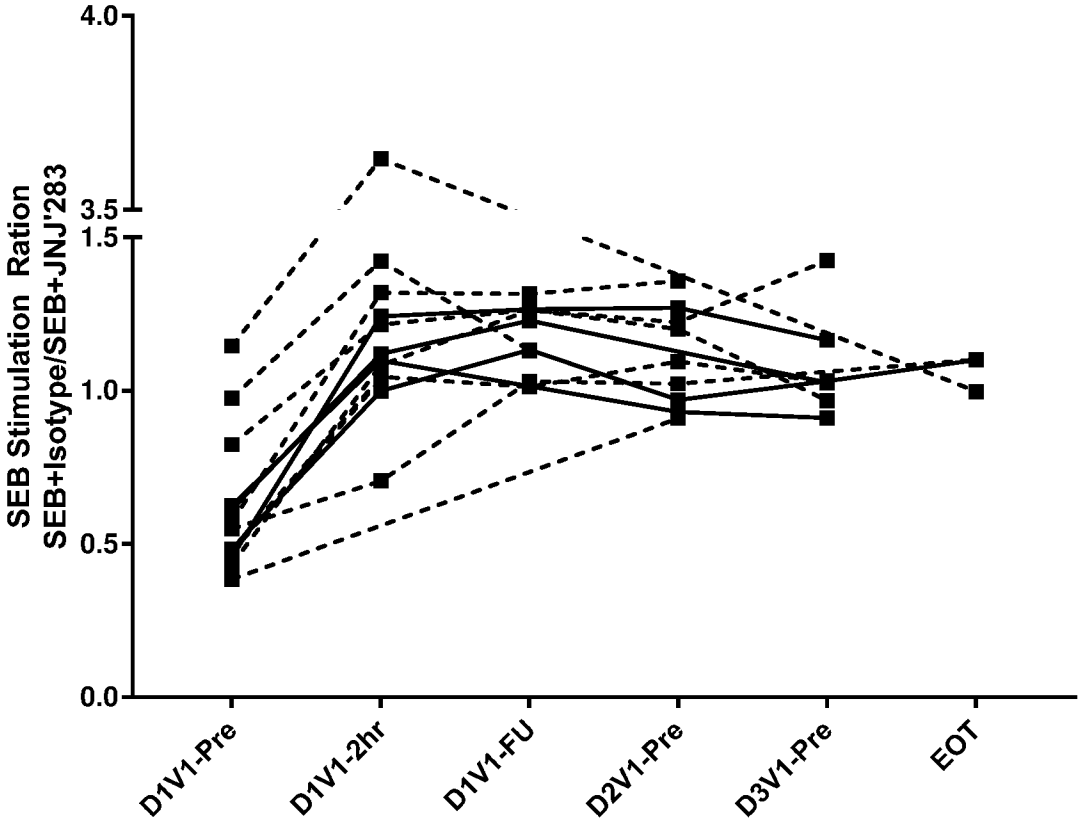

480 mg Q4W
% Receptor Occupancy
150
100
50
0
Dose 1 Pre
Dose 1 EOI+2H
Dose 1 Day 8
Dose 1 Day 15
Dose 1 Day 22
Dose 2 Pre
Dose 2 EOI+1H
Dose 3 Pre
Dose 5 Pre
Dose 5 EOI+1H
Dose 14Pre
EOT
Visit

FIG. 4


SEB Stimulation Ration
SEB+Isotype/SEB+JNJ'283
4.0
3.5
1.5
1.0
0.5
0.0
D1V1-Pre
D1V1-2hr
D1V1-FU
D2V1-Pre
D3V1-Pre
EOT