

**ANTI-PD-1-BASED TREATMENT BEFORE AND AFTER SURGERY****FIELD**

[0001] Disclosed herein is a method for the prevention, delay of progression or treatment of solid tumors, such as breast, colon and lung cancer (*e.g.*, non-small cell lung cancer) in a subject in need thereof comprising administering an antibody that binds to anti-PD-1, or a fragment thereof, as described herein (in particular using the doses and regimes of administration described herein), optionally in combination with a chemotherapy.

**REFERENCE TO AN ELECTRONIC SEQUENCE LISTING**

[0002] The contents of the electronic sequence listing (BEIG\_109\_00US\_SeqList\_ST26.xml; Size: 130,386 bytes; and Date of Creation: August 11, 2023) are incorporated by reference herein in their entirety.

**BACKGROUND**

[0003] Programmed death ligand 1 (PD-L1; also known as CD274 and B7-H1) is recognized as an important player in immune regulation and the maintenance of peripheral tolerance. Immune checkpoint therapies targeting PD-L1, or its receptor, PD-1, have resulted in groundbreaking improvements in clinical response in multiple human cancer types (*see, e.g.*, Brahmer et al., *N Engl J Med*, 366: 2455-2465 (2012); Robert et al., *N Engl J Med*, 372:320-330 (2015); Topalian et al., *N Engl J Med*, 366:2443-2454 (2012); Wolchok et al., *N Engl J Med*, 369:122-133 (2013)).

[0004] Tislelizumab (also known as BGB A317) is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against PD-1 that has been developed for the treatment of human malignancies in multiple organs and tissues. Tislelizumab binds to the extracellular domain of human PD-1 with high specificity and affinity, and competitively blocks the binding of both PD-L1 and programmed death ligand-2 (PD-L2). Unlike other PD-1 inhibitors, tislelizumab has been specifically engineered to remove the Fc and hinge regions to minimize Fcγ receptor binding on macrophages, which may abate potentially negative interactions.

[0005] Management of early and advanced solid tumors presents a major challenge and often consists of a combination of surgical, radiotherapeutic and systemic therapy approaches. Upfront

surgical treatment with or without adjuvant therapy, however, carries significant risks of morbidity and potential complications. With respect to non-small cell lung cancer (NSCLC), for example, although surgery is regarded as first-line option, only 25%–30% of NSCLCs are suitable for potentially curative resection. And despite optimal surgical management, the 5-year survival rate of resected NSCLC ranges between 73% for pathological stage Ia and 25% for pathological stage IIIa (Le Chevalier, T., 2010. *Annals of Oncology*, 21, pp.vii196-vii198). Thus, only a small proportion of patients with newly diagnosed lung tumors can receive curative surgery, and many of those have a high risk of postoperative recurrence.

[0006] Treatment before surgery (neoadjuvant) with chemotherapy and/or immunotherapy in the form of checkpoint inhibitors targeting the PD-1/PD-L1 axis, may be incorporated into the care of patients with early-stage solid tumors. The optimal timing of neoadjuvant and adjuvant immunotherapy treatment remains unclear. (Owen D., et al. *J Thorac Dis.* 2018 Feb;10(Suppl 3):S404-S411). With respect to NSCLC, for patients with cancer driver gene mutations, the disease-free survival (DFS) benefits of targeted immunotherapy have failed to translate into overall survival (OS) benefit. For patients without lung cancer driver gene mutations, chemotherapy has reached a plateau in improving efficacy and survival. (Bai, R. et al., 2020. *Frontiers in Oncology*, 10, p.575472).

[0007] Thus, there is a long-standing unmet need in the art to effectively treat solid tumors, such as breast, colon, and non-small cell lung cancer. In particular, there is a need to increase life span, survival rate and response to treatment in patients with early-stage operable disease.

#### SUMMARY

[0008] In some aspects, the present disclosure provides a method of treating a cancer in a subject in need thereof, wherein the cancer is a surgically resectable solid cancer, comprising:

(i) during a first treatment period parenterally administering to the subject a first dose of an anti-PD-1 antibody or an antigen-binding fragment thereof, wherein the first dose of the anti-PD-1 antibody is 200 mg (e.g., once every three-weeks);

(ii) after (i), surgically resecting the cancer of the subject; and

[0009] (iii) during a second treatment period after (ii) parenterally administering to the subject a second dose of the anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein

the second dose of the anti-PD-1 antibody is 400 mg (*e.g.*, once every 6 weeks) In some aspects, tumor lesions are measured by CT scan or X-ray before treatment and then after 200 mg at the time of surgery. In some aspects, the anti-PD-1 antibody or antigen-binding fragment thereof, comprises:

a VH CDR1, VH CDR2, and a VH CDR3 comprising amino acid sequences as set forth in SEQ ID Nos: 31, 32 and 33, and

a VL CDR1, VL CDR2, and a VL CDR3 comprising amino acid sequences as set forth in SEQ ID Nos: 34, 35 and 36.

**[0010]** In some aspects, the cancer is an early-stage cancer. In some aspects, the cancer is a Stage II or Stage IIIA cancer. In some aspects, the cancer is a Stage I cancer. In some aspects, the cancer is a Stage IIA cancer. In some aspects, the cancer is a Stage IIB cancer. In some aspects, the cancer is an mid-stage cancer. In some aspects, the cancer is an advanced stage or metastatic cancer (such as resectable advanced or metastatic cancer). In some aspects, the cancer is breast, colon or a lung cancer. In some aspects, the cancer is non-small cell lung cancer (NSCLC). In some aspects, the cancer is squamous cell carcinoma. In some aspects, the cancer is non-squamous cell carcinoma. In some aspects, the cancer is stage II or IIIA NSCLC. In some aspects, the cancer is not locally advanced or metastatic (*e.g.*, not locally advanced or metastatic NSCLC).

**[0011]** In some aspects, the heavy chain variable region of the anti-PD-1 antibody comprises the amino acid sequence of SEQ ID NO:24, and the light chain variable region of the anti-PD-1 antibody comprises the amino acid sequence of SEQ ID NO:26. In some aspects, the anti-PD-1 antibody comprises an IgG constant region comprising an amino acid sequence of SEQ ID NO:88. In some aspects, the anti-PD-1 antibody is administered intravenously, optionally wherein the administration is by IV infusion.

**[0012]** In some aspects, the subject has not been previously treated for the cancer or the treatment is a first-line therapy. In some aspects, the subject has not been previously treated with chemotherapy, radiotherapy and/or immunotherapy. In some aspects, the treatment is a second line therapy.

**[0013]** In some aspects, the first treatment period comprises 3 or 4 cycles of three-weeks

each. In some aspects, the second treatment period comprises less than or equal to 8 cycles of six weeks each. In some aspects, the second treatment period comprises at least 8 cycles of six weeks each. In some aspects, the second treatment period starts within 8 weeks of the surgical resecting.

[0014] In some aspects, the surgical resecting is followed by radiotherapy before the start of the second treatment period. In some aspects, the radiotherapy is administered 30 to 60 days after the surgical resecting, and the second treatment period starts between 7 and 30 days after the radiotherapy. In some aspects, the surgical resecting is not followed by radiotherapy. In some aspects, the second treatment period starts between 2 and 8 weeks after the surgical resection.

[0015] In some aspects, the first treatment period further comprises administering a therapeutically effective amount of one or more chemotherapeutic drugs. In some aspects, the one or more chemotherapeutic drugs comprises a platinum chemotherapy drug. In some aspects, the one or more chemotherapeutic drug is carboplatin or cisplatin. In some aspects, the cisplatin is administered intravenously at about 75 mg/m<sup>2</sup> or the carboplatin is administered intravenously at about area under the plasma or serum concentration-time curve 5 (AUC<sub>5</sub>), optionally wherein the administering is once every three-weeks (Q3W), optionally wherein the administration is by IV infusion.

[0016] In some aspects, the one or more chemotherapeutic drug further comprises pemetrexed or paclitaxel, optionally wherein the pemetrexed is used when the NSCLC is non-squamous and the paclitaxel is used when NSCLC is squamous. In some aspects, the pemetrexed is administered intravenously at about 500 mg/m<sup>2</sup>, optionally wherein the administering is once every three-weeks (Q3W), optionally wherein the administration is by IV infusion. In some aspects, the paclitaxel is administered intravenously at about 175 mg/m<sup>2</sup>, optionally wherein the administering is once every three-weeks (Q3W), optionally wherein the administration is by IV infusion.

[0017] In some aspects, the treating is clinically effective or the subject is a responder to the treating by at least one measure of response to treatment. In some aspects, the response to treatment is measured by overall survival, progression-free or event-free survival, major



pathological response (“MPR”), pathological complete response (“pCR”), overall response, partial response, duration of response, and/or tumor volume, diameter or size. A major pathological response (MPR) is defined as less than 10% residual viable tumor after neoadjuvant therapy. In some aspects, the treating results in the MPR in the subject. In some aspects, the MPR is at least twice that observed in the control group not treated with the anti-PD-1 antibody. In some aspects, the subject has at least 25%, 35%, 40%, 45% or 50% probability of the MPR. In some aspects, the treating is effective as demonstrated by patient population MPR of at least 25%, 35%, 40%, 45% or 50%. In some aspects, the response to treatment is measured by tumor volume, size or diameter, and wherein the treating reduces tumor volume, size or diameter in the subject by at least or more than 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85% or 90%. In some aspects, the treating results in the pCR in the subject. In some aspects, the subject has at least 15%, 20%, 25%, 30%, 35%, or 40% probability of the pCR, or the treating is effective as demonstrated by patient population pCR of at least 15%, 20%, 25%, 30%, 35%, or 40%.

**[0018]** In some aspects, the subject does not have an EGFR mutation, ROS1 mutation or an ALK gene translocation. In some aspects, the subject is EGFR negative for genomic tumor aberrations. In some aspects, the subject is negative for ALK genomic tumor aberrations.

**[0019]** In some aspects, the subject is a human. In some aspects, the human is an adult. In some aspects, the subject does not have a locally advanced cancer and/or metastatic cancer. In some aspects, the subject has liver, lung, lymph node, bone and/or adrenal gland metastasis, optionally wherein the subject has liver, lung and/or lymph node metastasis.

**[0020]** In another aspect, the present disclosure relates to a method of treating a cancer in a subject in need thereof, wherein: the cancer is a solid cancer, and the solid cancer is selected from the group consisting of a lung cancer, a breast cancer, and a colon cancer, the method comprises parenterally administering to the subject a dose of an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the dose is:

- (i) about 50 to 800 mg, or (ii) about 2 mg/kg to about 5 mg/kg; and
- the anti-PD-1 antibody comprises:

- (a) a VH CDR1, VH CDR2, and a VH CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:31, 32 and 33, and
- (b) a VL CDR1, VL CDR2, and a VL CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:34, 35 and 36.

**[0021]** In another aspect the present disclosure relates to a method of treating a cancer in a subject in need thereof, wherein the cancer is a solid cancer, comprising parenterally administering to the subject an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the anti-PD-1 antibody is administered:

- (i) at a dose from about 50 to 800 mg, or (ii) at a dose from about 2 mg/kg to about 5 mg/kg;

and the anti-PD-1 antibody comprises:

- (a) a VH CDR1, VH CDR2, and a VH CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:31, 32 and 33, and
- (b) a VL CDR1, VL CDR2, and a VL CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:34, 35 and 36; and the method further comprises administering a therapeutically effective amount of chemotherapeutic drugs comprising (i) a platinum chemotherapy drug, or (ii) carboplatin, and paclitaxel or nab-paclitaxel.

**[0022]** In some embodiments, the method further comprises administering a therapeutically effective amount of one or more chemotherapeutic drugs. In some embodiments, the one or more chemotherapeutic drugs comprises a platinum chemotherapy drug. In some embodiments, the one or more chemotherapeutic drugs comprises pemetrexed and a platinum chemotherapy drug. In some embodiments, the platinum chemotherapy drug is carboplatin or cisplatin. In some embodiments, the one or more chemotherapeutic drugs comprises (a) carboplatin, and (b) paclitaxel or nab-paclitaxel.

**[0023]** In some embodiments, the cancer is a lung cancer, wherein the lung cancer is locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC), wherein the lung cancer is negative for epidermal growth factor receptor (EGFR) aberrations and anaplastic

lymphoma kinase (ALK) genomic tumor aberrations, and the method further comprises administering pemetrexed and a platinum chemotherapy drug.

**[0024]** In some embodiments, the cancer is locally advanced or metastatic squamous non-small cell lung cancer (NSCLC), and the method further comprises administering (a) carboplatin, and (b) paclitaxel or nab-paclitaxel.

**[0025]** In some embodiments, the subject has not been previously treated for the cancer or the treatment is a first-line therapy. In some embodiments, the heavy chain variable region of the anti-PD-1 antibody comprises the amino acid sequence of SEQ ID NO:24, and the light chain variable region of the anti-PD-1 antibody comprises the amino acid sequence of SEQ ID NO:26. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising an amino acid sequence of SEQ ID NO:88. In some embodiments, the anti-PD-1 antibody is administered intravenously, optionally wherein the administration is by IV infusion. In some embodiments, the carboplatin is administered intravenously at about area under the plasma or serum concentration-time curve 5 (AUC5), optionally wherein the administering is once every three-weeks (Q3W), optionally wherein the administration is by IV infusion.

**[0026]** In some embodiments, the pemetrexed is administered intravenously at about 500 mg/m<sup>2</sup>, optionally wherein the administering is once every three-weeks (Q3W), optionally wherein the administration is by IV infusion. In some embodiments, the paclitaxel is administered intravenously at about 175 mg/m<sup>2</sup>, optionally wherein the administering is once every three-weeks (Q3W), optionally wherein the administration is by IV infusion.

**[0027]** In some embodiments, the anti-PD-1 antibody is administered at a dose from about 2 mg/kg to 5 mg/kg, optionally wherein the anti-PD-1 antibody is administered at a dose of about 2mg/kg Q3W, 5mg/kg Q3W or 200 mg Q3W, optionally wherein the anti-PD-1 antibody is administered at a dose of about 400 mg, optionally wherein the anti-PD-1 antibody is administered at a dose of about 150 mg Q2W, optionally wherein the anti-PD-1 antibody is administered at a dose of about 300 mg Q4W, and optionally wherein the anti-PD-1 antibody is administered at a dose of about 400 mg Q6W. In some embodiments, the anti-PD-1 antibody is administered at a dose from about 50 to 800 mg, optionally wherein the anti-PD-1 antibody is administered at 100 mg, 150 mg, 200, mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg,

550 mg, 600 mg, 650 mg, 700 mg, 750 mg, or 800 mg. In some embodiments, the PD-1 antibody is administered every week, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, or every 6 weeks, optionally wherein the anti-PD-1 antibody is administered at 150 mg every two weeks, 300 mg every four weeks, or 400 mg every six weeks. In some embodiments, the PD-1 antibody is administered at a first dose prior to surgical removal of the solid cancer, and wherein the PD-1 antibody is administered at a second dose after surgical removal of the solid cancer. In some embodiments, the first dose is:

- (i) about 50 to 800 mg, optionally wherein the anti-PD-1 antibody is administered at 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, or 800 mg, or
- (ii) about 2 mg/kg to about 5 mg/kg; optionally wherein the first dose is 200 mg once every three-weeks (Q3W);

and wherein the second dose is:

- (i) about 50 to 800 mg, optionally wherein the anti-PD-1 antibody is administered at 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, or 800 mg, or
- (ii) about 2 mg/kg to about 5 mg/kg; optionally wherein the first dose is 400 mg once every six weeks (Q6W).

[0028] In some embodiments, the solid cancer is an early-stage cancer.

[0029] In some embodiments, the solid cancer is a Stage II or Stage IIIA cancer.

[0030] In some embodiments, the solid cancer is not locally advanced or metastatic.

[0031] In some embodiments, the solid cancer is breast, colon or a lung cancer.

[0032] In some embodiments, the solid cancer is non-small cell lung cancer (NSCLC).

[0033] In some embodiments, the solid cancer is squamous cell carcinoma.

[0034] In some embodiments, the solid cancer is non-squamous cell carcinoma.

[0035] In some embodiments, the solid cancer is stage II or IIIA.

[0036] In some embodiments, the solid cancer is not locally advanced or metastatic.

[0037] In some embodiments, the solid cancer is esophageal squamous cell carcinoma.

[0038] In some embodiments, the anti-PD-1 antibody is formulated in a pharmaceutical composition comprising a histidine buffer, a surfactant, and a stabilizer. In some embodiments, the surfactant is a polysorbate. In some embodiments, the stabilizer is trehalose.

[0039] In another aspect, the present disclosure relates to a composition comprising an anti-PD-1 antibody for use in a method disclosed herein. In another aspect, the present disclosure provides an anti-PD-1 antibody for the manufacture of a medicament for use in a method disclosed herein.

[0040] Both the foregoing summary and the following brief description of the drawings and detailed description are exemplary and explanatory. They are intended to provide further details of the invention, but are not to be construed as limiting. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0041] **FIG. 1** is a schematic showing clinical trial treatment arms in a randomized, double-blind, placebo-controlled Phase 3 study to compare the efficacy and safety of neoadjuvant treatment with tislelizumab plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab treatment versus neoadjuvant treatment with placebo plus platinum-based doublet chemotherapy followed by placebo in patients with resectable Stage II or IIIA NSCLC. The study consisted of a screening phase, a treatment phase that included a neoadjuvant phase, surgery and an adjuvant phase, a safety follow-up phase, and a survival follow up phase. Abbreviations: AE, adverse event; d1, Day 1; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous(ly); N, number of patients; NSCLC, non-small cell lung cancer; Q3W, once every 3 weeks; Q6W, once every 6 weeks; Sq, Squamous; R, randomization ratio; R0, pathological complete resection of the primary tumor; WT, wild type.

[0042] **FIG. 2** Provides a table showing significant improvements in major pathological response (MPR) and pathological complete response (pCR) rates when comparing the efficacy of tislelizumab (*i.e.*, an anti-PD-1 antibody) + platinum doublet (*e.g.*, cisplatin or carboplatin +

etoposide) (Arm A) and placebo + platinum doublet (Arm B) as first-line treatment in 453 patients with treatment-naïve, resectable, confirmed squamous or non-squamous stage II-IIA NSCLC., in the study described in Example 1.

[0043] **FIG. 3** provides a schematic of a study design to evaluate tislelizumab plus chemotherapy/chemoradiotherapy as neoadjuvant treatment for resectable esophageal squamous cell carcinoma.

[0044] **FIGs. 4A-4B** show results of the percentage of residual viable tumor in responders (**FIG. 4A**) and non-responders (**FIG. 4B**).

[0045] **FIG. 5** shows the trial profile of the study of example 4. Across both treatment groups, of those patients who received PORT, seven were due to incomplete resection, and one was due to multiple pathologic N2 disease. ITT=intention-to-treat; PBO=placebo; PORT=postoperative radiotherapy; TIS=tislelizumab.

[0046] **FIG. 6** is a Kaplan-Meier plot of the ITT population. Kaplan-Meier plot of event-free survival assessed by blinded independent central review (ITT population) (A). Subgroup analysis of event-free survival (B). Data cutoff date: Aug 21, 2023. \*Excludes patients who were not evaluable/indeterminate. CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; EFS=event-free survival; HR=hazard ratio; ITT=intention-to-treat; NE=not estimable; NR=not reached; PBO=placebo; PD-L1=programmed cell death ligand-1; TIS=tislelizumab.

[0047] **FIG. 7** shows major pathological response rate and pathological complete response rate. Major pathological response rate assessed by blinded independent pathology review (**FIG. 7A**). Pathological complete response rate by blinded independent pathology review (**FIG. 7B**). \*MPR rate was defined as the proportion of patients with  $\leq 10\%$  residual viable tumour in the resected primary tumour and all resected lymph nodes after completion of neoadjuvant treatment, as assessed by blinded independent pathology review in the ITT population. Patients who did not receive surgical resection, or if a surgical specimen was not available, were considered as non-responders in the analysis. †pCR rate was defined as the proportion of patients absent of residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant treatment, as assessed by blinded independent pathology review in

the ITT population. Patients who did not receive surgical resection were considered as non-responders in the analysis. §Excludes patients who were not evaluable/indeterminate.

CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; ITT=intention-to-treat; MPR=major pathological response; OR=odds ratio; PBO=placebo; pCR=pathological complete response; PD-L1=programmed cell death ligand-1; TIS=tislelizumab.

[0048] **FIG. 8** shows subgroup analysis of pathological complete response. See legend to FIG. 7 for definitions of abbreviations.

[0049] **FIG. 9** shows Kaplan-Meier plot of overall survival in the ITT population. Overall Survival was defined as the time from the date of randomization to the date of death due to any cause. CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; NE=not estimable; NR=not reached; OS=overall survival; PBO=placebo; TIS=tislelizumab.

## DETAILED DESCRIPTION

### **I. Overview**

[0050] As detailed in the presently disclosed examples, it was surprisingly and unexpectedly discovered that the claimed methods result in effective treatment of solid cancer by treatment with an anti-PD-1 antibody according to the schedules and dosing regimens set forth herein. In particular, the present application provides the discovery of unexpected clinical benefits of the treatment regimen described herein before and/or after surgical removal of the solid cancer such as lung cancer, which historically has been difficult to treat.

[0051] In some aspects, provided herein are methods of treatment or delay or progression of solid cancer (*e.g.* a lung cancer, such as non-small cell lung cancer) in a subject (*e.g.*, human) by administering an anti-PD-1 antibody or an antigen-binding fragment thereof (*e.g.*, tislelizumab or an anti-PD-1 antibody having CDRs of the tislelizumab) and, optionally, chemotherapy (carboplatin, cisplatin, paclitaxel and/or pemetrexed). In some embodiments, the chemotherapy is carboplatin and/or cisplatin, and optionally further paclitaxel and/or pemetrexed (*e.g.*, paclitaxel if the cancer is a squamous cell carcinoma, and pemetrexed if the cancer is a non-squamous cell carcinoma).

[0052] In particular, the present disclosure relates to a method of treating a cancer in a subject in need thereof, wherein: the cancer is a solid cancer, and the solid cancer is selected from the group consisting of a lung cancer, a breast cancer, and a colon cancer, the method comprises parenterally administering to the subject a dose of an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the dose is:

(i) about 50 to 800 mg, or (ii) about 2 mg/kg to about 5 mg/kg;

and the anti-PD-1 antibody comprises:

(a) a VH CDR1, VH CDR2, and a VH CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:31, 32 and 33, and

(b) a VL CDR1, VL CDR2, and a VL CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:34, 35 and 36.

[0053] In another aspect the present disclosure relates to a method of treating a cancer in a subject in need thereof, wherein the cancer is a solid cancer, comprising parenterally administering to the subject an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the anti-PD-1 antibody is administered:

(i) at a dose from about 50 to 800 mg, or (ii) at a dose from about 2 mg/kg to about 5 mg/kg;

and the anti-PD-1 antibody comprises:

(a) a VH CDR1, VH CDR2, and a VH CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:31, 32 and 33, and

(b) a VL CDR1, VL CDR2, and a VL CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:34, 35 and 36; and the method further comprises administering a therapeutically effective amount of chemotherapeutic drugs comprising (i) a platinum chemotherapy drug, or (ii) carboplatin, and paclitaxel or nab-paclitaxel.

[0054] In some embodiments, the method further comprises administering a therapeutically effective amount of one or more chemotherapeutic drugs.

[0055] In some embodiments, provided herein are methods of treatment or delay or progression of a resectable solid cancer (*e.g.* a lung cancer, such as non-small cell lung cancer) in a subject (*e.g.*, human) by administering an anti-PD-1 antibody or an antigen-binding fragment



thereof (*e.g.*, tislelizumab or an anti-PD-1 antibody having CDRs of the tislelizumab) and, optionally, chemotherapy (carboplatin, cisplatin, paclitaxel and/or pemetrexed), followed by resection or surgical removal of the cancer.

[0056] In some embodiments, provided herein are methods of treatment or delay or progression of a resectable solid cancer (*e.g.* a lung cancer, such as non-small cell lung cancer) in a subject (*e.g.*, human) by administering a first dose of an anti-PD-1 antibody or an antigen-binding fragment thereof (*e.g.*, tislelizumab or an anti-PD-1 antibody having CDRs of the tislelizumab) and, optionally, chemotherapy (carboplatin, cisplatin, paclitaxel and/or pemetrexed), followed by resection of the cancer, and followed by administration of a second dose of the anti-PD-1 antibody or an antigen-binding fragment thereof. In some embodiments, the first dose of the anti-PD-1 antibody or fragment thereof is 200 mg, and the second dose of the anti-PD-1 antibody or fragment thereof is 400 mg. In some embodiments, the first dose is administered every 3 weeks (*e.g.*, for 2, 3, or 4 cycles). In some embodiments, the second dose is administered every 6 weeks (*e.g.*, for 6, 7, 8, 9 or 10 cycles or more).

[0057] In some embodiments, the solid cancer treated in accordance with the methods described herein is early- to mid-stage solid cancer, for example lung cancer (*e.g.*, non-small cell lung cancer).

[0058] In some embodiments, the solid cancer is a squamous cell carcinoma. In some embodiments, the solid cancer is a non-squamous cell carcinoma.

[0059] In some embodiments, the non-small cell lung cancer is a squamous cell carcinoma. In some embodiments, the non-small cell lung cancer is a non-squamous cell carcinoma.

[0060] In some embodiments, the solid cancer is esophageal squamous cell carcinoma.

[0061] In some embodiments, the therapy is a first-line therapy, *i.e.*, the subject has not been treated (*e.g.*, with chemotherapy and/or immunotherapy) for the cancer (*e.g.*, lung cancer).

[0062] In some embodiments, the subject has progressed after prior chemotherapy or did not tolerate prior chemotherapy.

[0063] In some embodiments, the human subject is a responder to treatment by at least one

measure of response to treatment. In some embodiments, the claimed therapy is effective in the treatment of solid cancer (*e.g.*, stage I, stage IIA, stage II or stage IIIA solid cancer, such as breast, colon or lung cancer). In some embodiments, the claimed therapy is effective in the treatment of the non-small cell lung cancer (*e.g.*, *e.g.*, stage I, stage IIA, stage II or stage IIIA non-small cell lung cancer).

**[0064]** The inventors of this application discovered unexpected clinical benefits of the treatment regimen described herein for specified populations of human patients with solid tumor types, such as, *e.g.*, non-small cell lung cancer. In particular, studies disclosed herein demonstrated significant improvements in event-free survival, major pathological response, and pathological complete response following perioperative tislelizumab combined with neoadjuvant chemotherapy. Hence, perioperative tislelizumab combined with neoadjuvant chemotherapy offered meaningful clinical benefit compared with neoadjuvant placebo plus chemotherapy. The disclosed phase 3 trial evaluated an extended dose interval for anti-PD-(L)1 antibodies in the perioperative setting, both as monotherapy and combined with chemotherapy, providing evidence that will broaden treatment options for patients with cancers such as NSCLC or ESCC.

**[0065] Experimental Results:** The surprising and unexpected nature of the invention described herein is detailed in the examples. In particular, Example 1 describes a randomized, double-blind, placebo-controlled, multicenter, Phase 3 study that was conducted, comparing the efficacy of tislelizumab (*i.e.*, an anti-PD-1 antibody) + platinum doublet (*e.g.*, cisplatin or carboplatin + etoposide) (Arm A) and placebo + platinum doublet (Arm B) as first-line treatment in 453 patients with treatment-naïve, resectable, confirmed squamous or non-squamous stage II-IIA NSCLC. The results showed that overall, Tislelizumab in combination with chemotherapy prior to surgery as first-line treatment for patients with untreated NSCLC demonstrated significant clinical benefit and a manageable safety profile compared to placebo plus chemotherapy alone prior to surgery.

**[0066]** Similarly, Example 3 describes an ongoing Phase 2, Multicenter, Open-Label, 2-cohort Study to investigate the efficacy and safety of positron emission tomography (PET) guided neoadjuvant treatment with Tislelizumab (BGB-A317) plus chemotherapy/chemoradiotherapy in patients R-ESCC. The purpose of this study was to evaluate

the pathological complete response (pCR) in participants receiving tislelizumab plus chemotherapy/chemoradiotherapy as neoadjuvant treatment. Example 3 detailed significant differences in MPR rates (exceeding 40.0%) and pCR rates (35.0%) favouring the tislelizumab group.

[0067] Finally, Example 4 describes a study demonstrating significant improvements in event-free survival, major pathological response, and pathological complete response following perioperative tislelizumab combined with neoadjuvant chemotherapy. Hence, perioperative tislelizumab combined with neoadjuvant chemotherapy offered meaningful clinical benefit as compared to neoadjuvant placebo plus chemotherapy. In the adjuvant setting, tislelizumab was administered at 400 mg on a 6-week cycle for up to eight cycles, providing a more flexible and convenient dosing schedule for patients than evaluated with other PD-(L)1 antibodies. This phase 3 trial evaluated an extended dose interval for anti-PD-(L)1 antibodies in the perioperative setting. Additionally, the safety profile of tislelizumab, both as monotherapy and when combined with chemotherapy, was manageable and consistent with the known safety profiles of the individual agents.

## **II. PD-1**

[0068] Programmed Death-1 (PD-1, also known as Programmed Death-1, PD1, Pcdcd-1 and CD279) is a 55 KD receptor protein related to CD28/CTLA4 co-stimulatory/inhibitory receptor family (Blank et al., 2005 *Cancer Immunol Immunother* 54:307-314). The genes and cDNAs coding for PD-1 were cloned and characterized in mouse and human (Ishida et al., 1992 *EMBO J* 11:3887-3395; Shinohara et al., 1994 *Genomics* 23:704-706). The full-length PD-1 contains 288 amino acid residues (NCBI accession number: NP\_005009). Its extracellular domain consists of amino acid residues 1-167, and the cytoplasmic C-terminal tail comprises residues 191-288, which has two hypothetical immune-regulatory motifs, an immunoreceptor tyrosine-based inhibitory motif (ITIM; Vivier et al., 1997 *Immunol Today* 18:286-291) and an immunoreceptor tyrosine switch motif (ITSM; Chemnitz et al., 2004 *J Immunol* 173:945-954).

[0069] To date, two sequence-related ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC), have been identified to specifically interact with PD-1, inducing intracellular signal transduction that inhibits CD3 and CD28 mediated T-cell activation (Riley, 2009 *Immunol Rev* 229:114-125),

which, in turn, attenuates T-cell activities, for example, reduction of cell proliferation, IL-2 and IFN- $\gamma$  secretion, as well as other growth factor and cytokine secretion.

**[0070]** Expression of PD-1 was frequently found in immune cells such as T-cells, B-cells, monocytes and natural killer (NK) cells. It was rarely expressed in other human tissues, such as muscle, epithelium, neuronal tissues, etc. Furthermore, high level of PD-1 expression is often associated with activation of immune cells. For example, when human T-cell line, Jurkat, was activated by phytohaemagglutinin (PHA) or phorbol ester (12-O-tetradecanoylphorbol-13-acetate, or TPA), the expression of PD-1 was up-regulated visible in Western Blot (Vibharka et al., 1997 *Exp Cell Res* 232:25-28). The same phenomenon was observed in stimulated murine T- and B-lymphocytes and in primary human CD4<sup>+</sup> T-cells upon stimulation by anti-CD3 antibody (Agata et al., 1996 *Int Immunol* 8:765-772; Bennett et al., 2003 *J Immunol* 170:711-118). The increase of PD-1 expression following stimulation of T effector cells redirects the activated T-effector cells towards exhaustion and reduced immune activities. Therefore, PD-1 mediated inhibitory signal plays an important role in immune tolerance (Bour-Jordan et al., 2011 *Immunol Rev* 241:180-205).

**[0071]** Increase of PD-1 expression in tumor-infiltrating lymphocytes (TILs) and PD-1 ligand expression in tumor cells were reported in varieties of cancers involved in different types of tissues and organs such as lung (Konishi et al., 2004 *Clin Cancer Res* 10:5094-5100), liver (Shi et al., 2008 *Int J Cancer* 128:887-896; Gao et al., 2009 *Clin Cancer Res* 15:971-979), stomach (Wu et al., 2006 *Acta Histochem* 108:19-24), kidney (Thompson et al., 2004 *Proc Natl Acad Sci* 101:17174-17179; Thompson et al., 2007 *Clin Cancer Res* 13:1757-1761), breast (Ghebeh et al., 2006 *Neoplasia* 8:190-198), ovary (Hamanishi et al. 2007 *Proc Natl Acad Sci* 104:3360-3365), pancreas (Nomi et al., 2007 *Clin Cancer Res* 13:2151-2157), melanocytes (Hino et al., 2010 *Cancer* 116:1757-1766) and esophagus (Ohigashi et al., 2005 *Clin Cancer Res* 11:2947-2953). More frequently, the increased expression of PD-1 and PD-L1 in those cancers is associated with poor prognosis of patient survival outcome. Transgenic mice with PD-1 gene knockout inhibiting xenograft cancer cell growth further elucidated the significance of PD-1 signaling in the modulation of immune system for cancer eradication or tolerance (Zhang et al., 2009 *Blood* 114:1545-1552).

[0072] PD-1 blockade can be accomplished by a variety of mechanisms including antibodies that bind PD-1 or its ligands. Examples of PD-1 and PD-L1 blockers, also named PD-1 and PD-L1 inhibitors, are described in US7488802; US7943743; US8008449; US8,168,757; US8217149, and WO03042402, WO2008156712, WO2010089411, WO2010036959, WO2011066342, WO2011159877, WO2011082400, WO2011161699, and WO2015035606, the entire contents of each of which are incorporated herein by reference.

(a) Anti-PD-1 Antibodies

[0073] In some embodiments, the methods described herein comprise administering an anti-PD-1 antibody or an antigen-binding fragment thereof. Any antibodies or antigen-binding fragments thereof that specifically bind to PD-1, particularly human PD-1, such as those described herein, can be used in compositions, combinations, uses and methods described herein.

[0074] In some embodiments, the anti-PD-1 antibody is any antibody known in the art or described herein. In some embodiments, the anti-PD-1 antibody is any antibody that specifically binds to PD-1. In some embodiments, the anti-PD-1 antibody inhibits PD-1-mediated cellular signaling and activity in immune cells. In some embodiments, the anti-PD-1 antibody binds to amino acid residues required for its ligand binding and/or inhibits ligand binding.

[0075] In some embodiments, the antibodies and fragments described herein are isolated and purified.

[0076] In some embodiments, the present disclosure is directed to an antibody or antigen-binding fragment thereof, wherein the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, a human engineered antibody, a single chain antibody (scFv), a Fab fragment, a Fab' fragment, or a F(ab')<sub>2</sub> fragment.

[0077] In some embodiments, the anti-PD-1 antibody is a monoclonal antibody. In some embodiments, the anti-PD-1 antibody is a humanized antibody. In some embodiments, the anti-PD-1 antibody is a human antibody. In some embodiments, the anti-PD-1 antibody is a chimeric antibody.

[0078] In some embodiments, described herein are anti-PD-1 antibody, wherein the antibody

is an immunoglobulin comprising any VH and VL regions described herein. The immunoglobulin molecules that can be used are of any type (*e.g.*, IgG, IgE, IgM, IgD, IgY, IgA). The immunoglobulin molecules that can be used are of any class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, IgA2). The immunoglobulin molecules that can be used are of any subclass.

[0079] In some embodiments, the anti-PD-1 antibody is an IgG4 antibody. In some embodiments, the present disclosure is directed to an antibody or antigen-binding fragment thereof, wherein the Fc domain is of an IgG4.

[0080] In some embodiments, the anti-PD-1 antibody is an IgG1 antibody. In some embodiments, the present disclosure is directed to an antibody or antigen-binding fragment thereof, wherein the Fc domain is of an IgG1.

[0081] In some embodiments, the anti-PD-1 antibody is a monoclonal humanized IgG1 antibody.

[0082] In some embodiments, the anti-PD-1 antibody is a monoclonal humanized IgG4 antibody.

[0083] In some embodiments, the contemplated anti-PD-1 antibodies and fragments comprise any CDRs described herein. In some embodiments, the contemplated anti-PD-1 antibodies and fragments comprise CDRs of any of the antibodies described herein. Complementarity-determining regions (CDRs) are defined in various ways in the art, including the Kabat, Chothia, AbM, Contact, and IMGT. In some embodiments, the CDRs of an antibody are defined according to the Kabat system.

[0084] In some embodiments, the contemplated anti-PD-1 antibodies and fragments comprise any light chain variable region described herein and/or any heavy chain variable region described herein. In some embodiments, the described anti-PD-1 antibodies and fragments comprise a light chain variable region having a sequence with at least 85%, 90% or 95% identity to any light chain variable region described herein and/or a heavy chain variable region having a sequence with at least 85%, 90% or 95% identity to any heavy chain variable region described herein. In some embodiments, the described anti-PD-1 antibodies and fragments comprise a light chain variable region having a sequence with at least 85%, 90% or 95% identity to any light

chain variable region described herein (with at least 90%, 95%, 97%, 99% or 100% identity in the CDR regions, *e.g.*, the six CDRs) and/or a heavy chain variable region having a sequence with at least 85%, 90% or 95% identity to any heavy chain variable region described herein (with at least 90%, 95%, 97%, 99% or 100% identity in the CDR regions, *e.g.*, the six CDRs). In some embodiments, the contemplated anti-PD-1 antibodies and fragments comprise light chain variable region and/or any heavy chain variable region of any antibody described herein.

[0085] In some embodiments, the anti-PD-1 antibody is any antibody described in WO2015/035606 A1 or US2015-0315274, the entire disclosures of which are incorporated by reference herein in their entireties, and in particular in respect to description therein of anti-PD-1 antibodies. In some embodiments, the anti-PD-1 antibody is any antibody described in any of: U.S. Patent Nos.: 8,735,553, 9,217,034, 9,834,606, 9,988,450, 10,519,235 and 11,186,637. U.S. Patent Nos.: 8,735,553, 9,217,034, 9,834,606, 9,988,450, 10,519,235 and 11,186,637 are incorporated by reference herein in their entireties, and in particular in respect to description therein of anti-PD-1 antibodies.

[0086] In some embodiments, the anti-PD-1 antibody is selected from one of the following: nivolumab (MDX 1106, BMS 936558, ONO-4538, Opdivo®) described in US8008449B2, a fully human IgG4 antibody that binds to and blocks the activation of PD-1 by its ligands PD-L1 and PD-L2; pembrolizumab (lambrolizumab, MK-3475 or SCH 900475, Keytruda®) disclosed in US8168757B2, a humanized monoclonal IgG4 antibody against PD-1; pidilizumab (CT-011), a humanized antibody that binds PD-1; AMP-224, a fusion protein of B7-DC; an antibody Fc portion; BMS-936559 (MDX-1105-01) for PD-L1 (B7-H1) blockade for PD-1 blockade. In some embodiments, the anti-PD-1 antibody is pembrolizumab, nivolumab, cemiplimab, dostarlimab, or retifanlimab.

[0087] In some embodiments, the anti-PD-1 antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vl) comprising any set of the complementarity determining regions (CDRs) listed below (with three Vh CDRs and three Vl CDRs):

|                |
|----------------|
| <b>Table 1</b> |
|----------------|

| Table 1    |                                                                                                                                               |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| a) mu317   | CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 12, 13, respectively);<br>and<br>CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 14, 15, 16, respectively); |
| b) mu326   | CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 18, 19, respectively);<br>and<br>CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively); |
| c) 317-4B6 | CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 31, 32, 33, respectively);<br>and<br>CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 34, 35, 36, respectively); |
| d) 326-4A3 | CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 37, 38, 39, respectively);<br>and<br>CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 40, 41, 42, respectively); |
| e) 317-1H  | CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 59, 13, respectively);<br>and<br>CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 14, 15, 16, respectively); |
| f) 317-4B2 | CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 60, 13, respectively);<br>and<br>CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 61, 15, 16, respectively); |
| g) 317-4B5 | CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 60, 13, respectively);<br>and<br>CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 61, 15, 16, respectively); |
| h) 317-4B6 | CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 32, 13, respectively);<br>and<br>CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 61, 15, 16, respectively); |
| i) 326-1   | CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively);<br>and<br>CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively); |
| j) 326-3B1 | CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively);                                                                             |



| Table 1       |                                                                                                                                                |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------|
|               | and<br>CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively);                                                                       |
| or k) 326-3G1 | CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively);<br>and<br>CDR-L1, CDR-I 2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively). |

**[0088]** In some embodiments, the anti-PD-1 antibody comprises a heavy chain variable region (Vh) comprising complementarity determining regions (CDRs) CDR-H1, CDR-H2 and CDR-H3 of SEQ ID NOs: 31, 32, 33, respectively, and a light chain variable region (Vl) comprising CDRs CDR-L1, CDR-L2 and CDR-L3 of SEQ ID NOs: 34, 35, 36, respectively. In some embodiments, the anti-PD-1 antibody comprises Vh and Vl CDRs of the 317-4B6 antibody described herein.

**[0089]** In some embodiments, the anti-PD-1 antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vl) that contain any combinations of the CDRs listed below (with three Vh CDRs and three Vl CDRs):

| Table 2 |                                                                                                                                                                               |
|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (a)     | CDR-H1 (SEQ ID NO 31), CDR-H2 (SEQ ID NO 12, 32, 59 or 60) and CDR-H3 (SEQ ID NO 33),<br>CDR-L1 (SEQ ID NO 14, 34 or 61), CDR-L2 (SEQ ID NO 35) and CDR-L3 (SEQ ID NO 36); or |
| (b)     | CDR-H1 (SEQ ID NO 37), CDR-H2 (SEQ ID NO 18, 38 or 62) and CDR-H3 (SEQ ID NO 39),<br>CDR-L1 (SEQ ID NO 40), CDR-L2 (SEQ ID NO 41) and CDR-L3 (SEQ ID NO 42).                  |

**[0090]** In some embodiments, the anti-PD-1 monoclonal antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vl) comprising:

**Table 3**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>a) mu317 (SEQ ID NOs: 4 and 6, respectively);</p> <p>b) mu326 (SEQ ID NOs: 8 and 10, respectively);</p> <p>c) 317-4B6 (SEQ ID NOs: 24 and 26, respectively);</p> <p>d) 326-4A3 (SEQ ID NOs: 28 and 30, respectively);</p> <p>e) 317-4B2 (SEQ ID NOs: 43 and 44, respectively);</p> <p>f) 317-4B5 (SEQ ID NOs: 45 and 46, respectively);</p> <p>g) 317-1 (SEQ ID NOs: 48 and 50, respectively);</p> <p>h) 326-3B1 (SEQ ID NOs: 51 and 52, respectively);</p> <p>i) 326-3GI (SEQ ID NOs: 53 and 54, respectively);</p> <p>j) 326-1 (SEQ ID NOs: 56 and 58, respectively);</p> <p>k) 317-3A1 (SEQ ID NOs: 64 and 26, respectively);</p> <p>l) 317-3C1 (SEQ ID NOs: 65 and 26, respectively);</p> <p>m) 317-3E1 (SEQ ID NOs: 66 and 26, respectively);</p> <p>n) 317-3F1 (SEQ ID NOs: 67 and 26, respectively);</p> | <p>p) 317-3H1 (SEQ ID NOs: 69 and 26, respectively);</p> <p>q) 317-311 (SEQ ID NOs: 70 and 26, respectively);</p> <p>r) 317-4B 1 (SEQ ID NOs: 71 and 26, respectively);</p> <p>s) 317-4B3 (SEQ ID NOs: 72 and 26, respectively);</p> <p>t) 317-4B4 (SEQ ID NOs: 73 and 26, respectively);</p> <p>u) 317-4A2 (SEQ ID NOs: 74 and 26, respectively);</p> <p>v) 326-3 A 1 (SEQ ID NOs: 75 and 30, respectively);</p> <p>w) 326-3C1 (SEQ ID NOs: 76 and 30, respectively);</p> <p>x) 326-3D1 (SEQ ID NOs: 77 and 30, respectively);</p> <p>y) 326-3E1 (SEQ ID NOs: 78 and 30, respectively);</p> <p>z) 326-3F1 (SEQ ID NOs: 79 and 30, respectively);</p> <p>aa) 326-3B N55D (SEQ ID NOs: 80 and 30, respectively);</p> <p>ab) 326-4A1 (SEQ ID NOs: 28 and 81, respectively); or</p> <p>ac) 326-4A2 (SEQ ID NOs: 28 and 82, respectively);</p> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| Table 3                                           |                |
|---------------------------------------------------|----------------|
| o) 317-3G1 (SEQ ID NOs: 68 and 26, respectively); | respectively). |

[0091] In some embodiments, the anti-PD-1 antibody comprises a heavy chain variable region (Vh) comprising the amino acid sequence of SEQ ID NO:24 and a light chain variable region (Vl) comprising the amino acid sequence of SEQ ID NO:26. In some embodiments, the anti-PD-1 antibody comprises the Vh and Vl of the 317-4B6 antibody described herein.

[0092] In some embodiments, the anti-PD-1 antibody comprises a heavy chain variable region (Vh) comprising an amino acid sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 % identical to the amino acid sequence of SEQ ID NO:24 and a light chain variable region (Vl) comprising an amino acid sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 % identical to the amino acid sequence of SEQ ID NO:26.

[0093] In some embodiments, the anti-PD-1 antibody comprises a heavy chain variable region (Vh) or light chain variable region (Vl) encoded by the cDNA of one of more of SEQ ID NO:23, 25, 27, 29, 47, 49, 55, 57.

[0094] In some embodiments, the antibody comprises an IgG4 Fc region having a serine to proline mutation at position 228 (EU numbering system). In some embodiments, this mutation is referred to as the S228P mutation. In some embodiments, the antibody comprises an IgG4 Fc region having a mutation at one or more of positions 233, 234, 235, 265, 309, and 409 (EU numbering system). For example, in some embodiments, the antibody comprises an IgG4 region having a mutation at 228 and at least one other position, wherein the at least one other mutation results in reduced binding to one or more FcγR. In further embodiments, the antibody comprises an IgG4 region having a mutation at position 228 and at least two, at least 3, at least 4, at least 5, or at least 6 additional positions, wherein one or more of the additional mutations results in reduced binding to one or more FcγR. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 234 and 235. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 233, 235, and 235. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 234, 235, and 265. In some

embodiments, the antibody comprises an IgG4 region having mutations at positions 233, 234, 235, and 265. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 234, 235, 265, and 409. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 233, 234, 235, 265, and 409. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 234, 235, 265, 309, and 409. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 233, 234, 235, 265, 309, and 409. The mutation at position 234 may be a phenylalanine to valine substitution or a phenylalanine to alanine substitution. The mutation at position 235 may be a leucine to alanine substitution. The mutation at position 233 may be a glutamic acid to proline substitution. The mutation at position 265 may be a aspartic acid to valine substitution or an aspartic acid to threonine substitution. The mutation at position 309 may be a leucine to valine substitution. The mutation at position 409 may be an arginine to a lysine, threonine, or methionine substitution.

**[0095]** In some embodiments, the anti-PD-1 antibody is an antibody which comprises a IgG4 heavy chain effector or constant domain comprising any of SEQ ID NOs: 83-88 or 91-106. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising any one of the amino acid sequences: SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87 and SEQ ID NO:88. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising any one of the amino acid sequences: SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105 and SEQ ID NO:106. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:83. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:84. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:85. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:86. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:87. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:88. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region

comprising SEQ ID NO:91. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:92. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:93. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:94. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:95. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:96. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:97. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:98. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:99. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:100. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:101. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:102. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:103. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:104. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:105. In some embodiments, the anti-PD-1 antibody comprises an IgG constant region comprising SEQ ID NO:106.

[0096] In some embodiments, the anti-PD-1 antibody is an antibody which contains a F(ab) or F(ab)<sub>2</sub> comprising a heavy chain variable region (V<sub>h</sub>), a light chain variable region (V<sub>l</sub>) and a IgG4 heavy chain effector or constant domain.

[0097] In some embodiments, the anti-PD-1 antibody is an antibody which comprises a heavy chain variable region (V<sub>h</sub>) and a light chain variable region (V<sub>l</sub>), and a IgG4 heavy chain effector or constant domain comprising SEQ ID NOs:87 or 88, wherein the heavy chain variable region (V<sub>h</sub>) and the light chain variable region (V<sub>l</sub>) comprise:

| Table 4                                      |                                                  |
|----------------------------------------------|--------------------------------------------------|
| a) mu317 (SEQ ID NOs:4 and 6, respectively); | p) 317-3H1 (SEQ ID NOs:69 and 26, respectively); |

| Table 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| b) mu326 (SEQ ID NOs:8 and 10, respectively);<br>c) 317-4B6 (SEQ ID NOs:24 and 26, respectively);<br>d) 326-4A3 (SEQ ID NOs:28 and 30, respectively);<br>e) 317-4B2 (SEQ ID NOs:43 and 44, respectively);<br>f) 317-4B5 (SEQ ID NOs:45 and 46, respectively);<br>g) 317-1 (SEQ ID NOs:48 and 50, respectively);<br>h) 326-3B1 (SEQ ID NOs:51 and 52, respectively);<br>i) 326-3GI (SEQ ID NOs:53 and 54, respectively);<br>j) 326-1 (SEQ ID NOs:56 and 58, respectively);<br>k) 317-3A1 (SEQ ID NOs:64 and 26, respectively);<br>l) 317-3C1 (SEQ ID NOs:65 and 26, respectively);<br>m) 317-3E1 (SEQ ID NOs: 66 and 26, respectively);<br>n) 317-3F1 (SEQ ID NOs: 67 and 26, respectively);<br>o) 317-3G1 (SEQ ID NOs:68 and 26, respectively); | q) 317-311 (SEQ ID NOs:70 and 26, respectively);<br><br>r) 317-4B 1 (SEQ ID NOs:71 and 26, respectively);<br>s) 317-4B3 (SEQ ID NOs:72 and 26, respectively);<br>t) 317-4B4 (SEQ ID NOs:73 and 26, respectively);<br>u) 317-4A2 (SEQ ID NOs:74 and 26, respectively);<br>v) 326-3 A 1 (SEQ ID NOs:75 and 30, respectively);<br>w) 326-3C1 (SEQ ID NOs:76 and 30, respectively);<br>x) 326-3D1 (SEQ ID NOs: 77 and 30, respectively);<br>y) 326-3E1 (SEQ ID NOs:78 and 30, respectively);<br>z) 326-3F1 (SEQ ID NOs:79 and 30, respectively);<br>aa) 326-3B N55D (SEQ ID NOs:80 and 30, respectively);<br>ab) 326-4A1 (SEQ ID NOs:28 and 81, respectively); or<br>ac) 326-4A2 (SEQ ID NOs:28 and 82, respectively). |

**[0098]** In some embodiments, the anti-PD-1 antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vl), and a IgG4 heavy chain effector or constant domain comprising SEQ ID NOs:88.

**[0099]** In some embodiments, the anti-PD-1 antibody is an antibody which comprises a heavy chain CDR-H1, CDR-H2, and CDR-H3 according to SEQ ID NOs: 11, 32, and 13,

respectively; and a light chain CDR-L1, CDR-L2, and CDR-L3 according to SEQ ID NOs:61, 15, and 16, respectively.

**[00100]** In some embodiments, the anti-PD-1 antibody is an antibody which comprises a heavy chain CDR-H1, CDR-H2 and CDR-H3 according to SEQ ID NOs:31, 32, 33, respectively; and a light chain CDR-L1, CDR-L2 and CDR-L3 according to SEQ ID NOs:34, 35, 36, respectively. In some embodiments, the anti-PD-1 monoclonal antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vl) comprising SEQ ID NO:24 and SEQ ID NO:26, respectively.

**[00101]** In some embodiments, the anti-PD-1 antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vl) (comprising SEQ ID NO:24 and SEQ ID NO:26, respectively) and a IgG4 heavy chain effector or constant domain (comprising SEQ ID NO:88). In some embodiments, the anti-PD-1 antibody specifically binds to PD-1, such as to PD-1 residues including K45 and I93; or I93, L95 and P97, and inhibits PD-1-mediated cellular signaling and activities in immune cells, with the antibody binding to a set of amino acid residues required for its ligand binding.

**[00102]** In any of the above-described embodiments, the anti-PD-1 antibody can be monoclonal. In some embodiments, the antibody is monoclonal and humanized. In some embodiments, the antibody is monoclonal, humanized, IgG4 antibody. In some embodiments, the anti-PD-1 antibody is a monoclonal antibody or a fragment thereof, comprising a heavy chain variable region (Vh) amino acid sequence of SEQ ID NO:24, a light chain variable region (Vl) amino acid sequence of SEQ ID NO:26, and an IgG4 constant domain amino acid sequence of SEQ ID NO:88. In some embodiments, the anti-PD-1 antibody is Tislelizumab. The sequence of Tislelizumab is known in the art.

**[00103]** In some embodiments, the present disclosure provides for anti-PD1 antibodies and antigen-binding fragments thereof having the sequences provided in the Table below. In some embodiments, the anti-PD1 antibody or antigen-binding fragment thereof specifically binds human PD1 and comprises the six CDRs provided in the Table below. In some embodiments, the anti-PD1 antibody or antigen-binding fragment thereof specifically binds human PD1 and comprises a heavy chain variable region and a light chain variable region comprising the

sequences provided in the Table below. In some embodiments, the anti-PD1 antibody comprises an IgG4 constant domain comprising any of the sequences provided below. In some embodiments, the IgG4 constant domain comprises one of the last two sequences provided in Table 5.

| <b>Table 5: Sequences of anti-PD1 antibody</b> |                   |                                                                                                                                                                                                                                                                                                                                                                          |
|------------------------------------------------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Domain</b>                                  | <b>SEQ ID NO:</b> | <b>Amino Acid Sequence</b>                                                                                                                                                                                                                                                                                                                                               |
| CDR-H1                                         | SEQ ID NO:31      | GFSLTSYGVH                                                                                                                                                                                                                                                                                                                                                               |
| CDR-H2                                         | SEQ ID NO:32      | VIYADGSTNYPNPSLKS                                                                                                                                                                                                                                                                                                                                                        |
| CDR-H3                                         | SEQ ID NO:33      | ARAYGNWYIDV                                                                                                                                                                                                                                                                                                                                                              |
| CDR-L1                                         | SEQ ID NO:34      | KSESVSNDVA                                                                                                                                                                                                                                                                                                                                                               |
| CDR-L2                                         | SEQ ID NO:35      | YAFHRFT                                                                                                                                                                                                                                                                                                                                                                  |
| CDR-L3                                         | SEQ ID NO:36      | HQAYSSPYT                                                                                                                                                                                                                                                                                                                                                                |
| Vh                                             | SEQ ID NO:24      | QVQLQESGPGLVKPSSETLSLTCTVSGFSLTSYGVHWIRQ<br>PPGKGLEWIGVIYADGSTNYPNPSLKSRTISKDTSKNQV<br>SLKLSSVTAADTAVYYCARAYGNWYIDVWGQGTTV<br>TVSS                                                                                                                                                                                                                                       |
| VI                                             | SEQ ID NO:26      | DIVMTQSPDSLAVSLGERATINCKSESVSNDVAWYQQ<br>KPGQPPKLLINYAFHRFTGVPDRFSGSGYGTDFLTISLL<br>QAEDVAVYYCHQAYSSPYTFGQGTKLEIK                                                                                                                                                                                                                                                        |
| IgG4<br>constant<br>domain                     | SEQ ID NO:27      | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV<br>SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT<br>KTYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPEFEG<br>GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF<br>NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ<br>DWLNGKEYK<br>CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT<br>KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPV<br>LSDSGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHN<br>HYTQKSLSLSLGK |
| IgG4<br>constant<br>domain                     | SEQ ID NO:28      | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV<br>SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT<br>KTYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPPVAG<br>GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF<br>NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ<br>DWLNGKEYK<br>CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT<br>KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPV<br>LSDSGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHN<br>HYTQKSLSLSLGK |
| IgG4<br>constant<br>domain                     | SEQ ID NO:29      | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV<br>SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT<br>KTYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPPVAG<br>GPSVFLFPPKPKDTLMISRTPEVTCVVVAVSQEDPEVQF<br>NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ<br>DWLNGKEYK                                                                                                                                              |



| Table 5: Sequences of anti-PD1 antibody |              |                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------------------------------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Domain                                  | SEQ ID NO:   | Amino Acid Sequence                                                                                                                                                                                                                                                                                                                                                      |
|                                         |              | CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT<br>KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPV<br>LSDGGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHN<br>HYTQKSLSLSLGK                                                                                                                                                                                                                                |
| IgG4<br>constant<br>domain              | SEQ ID NO:30 | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV<br>SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGT<br>KTYTCNVDPKPSNTKVDKRVEKYGPPCPPCPAPPVAG<br>GPSVFLFPPKPKDTLMISRTPEVTCVVVTVSQEDPEVQF<br>NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ<br>DWLNGKEYK<br>CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT<br>KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPV<br>LSDGGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHN<br>HYTQKSLSLSLGK |
| IgG4<br>constant<br>domain              | SEQ ID NO:31 | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV<br>SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGT<br>KTYTCNVDPKPSNTKVDKRVEKYGPPCPPCPAPPVAG<br>GPSVFLFPPKPKDTLMISRTPEVTCVVVAVSQEDPEVQF<br>NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ<br>DWLNGKEYK<br>CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT<br>KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPV<br>LSDGGSFFLYSKLTVDKSRWQEGNVFSCSVMEALHN<br>HYTQKSLSLSLGK |
| IgG4<br>constant<br>domain              | SEQ ID NO:32 | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV<br>SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGT<br>KTYTCNVDPKPSNTKVDKRVEKYGPPCPPCPAPPVAG<br>GPSVFLFPPKPKDTLMISRTPEVTCVVVAVSQEDPEVQF<br>NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVVHQ<br>DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY<br>TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP<br>ENNYKTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSC<br>SVMEALHNHYTQKSLSLSLGK     |

[00104] In some embodiments, the anti-PD1 antibodies or antigen-binding fragments thereof include amino acids that have been mutated, yet have at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% percent identity in the CDR regions with the CDR regions depicted in the sequences described herein, such as in the Table above. In some aspects, it includes mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the CDR regions when compared with the CDRs disclosed herein.

[00105] In some embodiments, the anti-PD1 antibodies include those where the amino acids

or nucleic acids encoding the amino acids have been mutated; yet have at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% percent identity to the sequences described herein (*e.g.*, in the heavy and light chain variable regions and/or IgG constant regions), such as in the Table above. In some aspects, it includes mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the heavy and light chain variable regions when compared with the heavy and light chain variable regions in the sequence disclosed herein, while retaining substantially the same therapeutic activity.

[00106] The anti-PD-1 antibodies and antigen-binding fragments thereof described herein can be made by any method known in the art and/or described herein. Methods of making monoclonal antibodies are well known in the art. See *e.g.*, Harlow E and Lane D, *Antibodies: A Laboratory Manual* (Cold Spring Harbor Press, 2nd ed. 1988); Hammerling GJ et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563 (Elsevier, NY, 1981); Kohler G and Milstein C, 1975, *Nature* 256:495; Goding JW (Ed), *Monoclonal Antibodies: Principles and Practice*, pp. 59-103 (Academic Press, 1986). Methods of making humanized antibodies are also well known in the art. See, *e.g.*, Padlan EA (1991) *Mol Immunol* 28(4/5): 489-498; Studnicka GM et al, (1994) *Prot Engineering* 7(6): 805-814; and Roguska MA et al, (1994) *PNAS* 91 : 969-973; Tan P et al, (2002) *J Immunol* 169: 1119-25; Caldas C et al, (2000) *Protein Eng.* 13(5): 353-60; Morea V et al, (2000), *Methods* 20(3): 267-79; Baca M et al, (1997) *J Biol Chem* 272(16): 10678-84; Roguska MA et al, (1996) *Protein Eng* 9(10): 895-904; Couto JR et al, (1995) *Cancer Res.* 55 (23 Supp): 5973s-5977s; Couto JR et al, (1995) *Cancer Res* 55(8): 1717-22; Sandhu JS (1994) *Gene* 150(2): 409-10; Pedersen JT et al, (1994) *J Mol Biol* 235(3): 959-73). Methods of making human antibodies are also known in the art. See, *e.g.*, International Publication Nos. WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741.

[00107] The anti-PD1 monoclonal antibodies and antibody fragments thereof may be prepared in accordance with the disclosure of WO2015/035606A1 or US 2015-0315274, the entire disclosures of which are incorporated by reference herein.

(b) Anti-PD-1 Antibody Dosing and Administration

[00108] In some embodiments, the anti-PD-1 antibody (*e.g.*, any of the antibodies described herein) is administered by any suitable means. In some embodiments, the anti-PD-1 antibody is administered parenterally. In some embodiments, the anti-PD-1 antibody is administered intravenously (IV). In some embodiments, the anti-PD-1 antibody is administered by IV infusion. In some embodiments, the anti-PD-1 antibody is infused over 60 minutes or more. In some embodiments, the anti-PD-1 antibody is infused over 30 minutes or more. In some embodiments, the anti-PD-1 antibody is administered subcutaneously. In some embodiments, the anti-PD-1 antibody is administered intramuscularly. In some embodiments, the anti-PD-1 antibody is administered peritoneally.

[00109] In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered parenterally. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered intravenously (IV). In some embodiments, Tislelizumab is administered by IV infusion. In some embodiments, the IV infusion is over 60 minutes or more. In some embodiments, the IV infusion is over 30 minutes or more.

[00110] In some embodiments, the anti-PD-1 antibody (*e.g.*, any of the antibodies described herein) is administered at a fixed dose. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered at a fixed dose.

[00111] In some embodiments, the anti-PD-1 antibody is administered at a dose of 200 mg or about 200 mg. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered at a dose of 200 mg or about 200 mg. In some embodiments, Tislelizumab is administered at a dose of 200 mg.

[00112] In some embodiments, the anti-PD-1 antibody is administered at a dose from about 2 mg/kg to about 200 mg/kg (and any value in between). In some embodiments, the anti-PD-1 antibody is administered at a dose from about 2 mg/kg to about 5 mg/kg (*e.g.*, 2 mg/kg to 5

mg/kg). In some embodiments, the anti-PD-1 antibody is administered at a dose of 2 mg/kg, 2.5 mg/kg, 3 mg/kg, 3.5 mg/kg, 4 mg/kg, 4.5 mg/kg, or 5 mg/kg (or any value in between these values). In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the VI of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered at a dose from about 2 mg/kg to about 5 mg/kg (*e.g.*, 2 mg/kg to 5 mg/kg). In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the VI of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered at a dose of 2 mg/kg, 2.5 mg/kg, 3 mg/kg, 3.5 mg/kg, 4 mg/kg, 4.5 mg/kg, or 5 mg/kg (or any value in between these values). In some embodiments, Tislelizumab is administered at a dose of 2 mg/kg to 5 mg/kg.

[00113] In some embodiments, the anti-PD-1 antibody is administered at a dosage of about 2 mg/kg Q3W to about 200 mg/kg once every three-weeks (Q3W). In some embodiments, the anti-PD-1 antibody is administered at a dosage of about 2mg/kg Q3W, 5mg/kg Q3W or 200 mg flat Q3W.

[00114] In some embodiments, the anti-PD-1 antibody is administered once every three-weeks. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the VI of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered once every three-weeks (*e.g.*, in 200 mg dose). In some embodiments, Tislelizumab is administered at dose from about 50 to 800 mg, optionally wherein the anti-PD-1 antibody is administered at 100 mg, 150 mg, 200, mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, or 800 mg. In some embodiments, the PD-1 antibody is administered every week, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, or every 6 weeks, preferably wherein the anti-PD-1 antibody is administered at 150 mg every two weeks, 300 mg every four weeks, or 400 mg every six weeks.

[00115] In some embodiments, the anti-PD-1 antibody is administered once every three-weeks for 4 cycles or at least 4 cycles. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the VI of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered once every three-weeks for 4 cycles or at least 4 cycles (*e.g.*, in 200 mg dose).

[00116] In some embodiments, the anti-PD-1 antibody is administered once every three-weeks for 3 cycles or at least 3 cycles. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered once every three-weeks for 3 cycles or at least 3 cycles (*e.g.*, in 200 mg dose).

[00117] In some embodiments, the anti-PD-1 antibody is administered at a dose of 400 mg or about 400 mg. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered at a dose of 400 mg or about 400 mg. In some embodiments, Tislelizumab is administered at a dose of 400 mg.

[00118] In some embodiments, the anti-PD-1 antibody is administered at a dose more than about 200 mg/kg to about 400 mg/kg.

[00119] In some embodiments, the anti-PD-1 antibody is administered at a dosage of about 400 mg/kg once every six-weeks (Q6W). In some embodiments, the anti-PD-1 antibody is administered at a dosage of about 400 mg flat Q6W.

[00120] In some embodiments, the anti-PD-1 antibody is administered once every six-weeks. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered once every six-weeks (*e.g.*, in 400 mg dose).

[00121] In some embodiments, the anti-PD-1 antibody is administered once every six-weeks for 8 cycles or at least 8 cycles. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered once every six-weeks for 8 cycles or at least 8 cycles (*e.g.*, in 400 mg dose).

[00122] In some embodiments, the anti-PD-1 antibody is administered once every six-weeks for less than 8 cycles. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered once every six-weeks for less than 8 cycles (*e.g.*, in 400 mg

dose).

[00123] In some embodiments, the anti-PD-1 antibody is administered in one treatment cycle. In some embodiments, the anti-PD-1 antibody is administered in two treatment cycles. In some embodiments, the anti-PD-1 antibody is administered in three treatment cycles. In some embodiments, the anti-PD-1 antibody is administered in four treatment cycles. In some embodiments, the anti-PD-1 antibody is administered in five treatment cycles. In some embodiments, the anti-PD-1 antibody is administered in six treatment cycles. In some embodiments, the anti-PD-1 antibody is administered in seven treatment cycles. In some embodiments, the anti-PD-1 antibody is administered in eight treatment cycles. In some embodiments, the anti-PD-1 antibody is administered in nine treatment cycles. In some embodiments, the anti-PD-1 antibody is administered in ten treatment cycles. In some embodiments, the anti-PD-1 antibody is administered in eleven treatment cycles. In some embodiments, the anti-PD-1 antibody is administered in twelve treatment cycles. In some embodiments, the anti-PD-1 antibody is administered in thirteen treatment cycles. In some embodiments, the anti-PD-1 antibody is administered in fourteen treatment cycles. In some embodiments, the anti-PD-1 antibody is administered in fifteen treatment cycles. In some embodiments, a treatment cycle is three-weeks. In some embodiments, a treatment cycle is six-weeks.

[00124] In some embodiments, the anti-PD-1 antibody is administered on Day 1 of the cycle (*e.g.*, Day 1 of 21 day or 3-week cycle, or Day 1 of 42 day or 6-week cycle).

[00125] In some embodiments, the anti-PD-1 antibody is IV infused over 60 minutes or more (*e.g.*, in the neoadjuvant phase). In some embodiments, the anti-PD-1 antibody is IV infused over 60 minutes or more in cycle 1, and IV infused over 30 minutes or about 30 minutes in subsequent cycles (*e.g.*, cycles 2 to 4, cycles 2 to 5, or any number of cycles after the first cycle). In some embodiments, the anti-PD-1 antibody is IV infused over 60 minutes or more in cycle 1, and IV infused over less than 60 minutes in subsequent cycles (*e.g.*, cycles 2 to 4, cycles 2 to 5, or any number of cycles after the first cycle). In some embodiments, the infusion time for the anti-PD-1 antibody is reduced from 60 minutes to 30 minutes if, and only if, the 60-minute infusion time is well tolerated by the treated subject. In some embodiments, during the adjuvant

phase, the anti-PD-1 antibody is IV infused over 90 minutes or more (at least in cycle 1 of the adjuvant phase). In some embodiments, during the adjuvant phase, the infusion time for the anti-PD-1 antibody is reduced from 90 minutes to 60 minutes to 30 minutes if, and only if, the longer infusion time is well tolerated by the treated subject.

**[00126]** In some embodiments, the anti-PD-1 antibody is administered in an induction treatment period (or neoadjuvant phase). In some embodiments, the anti-PD-1 antibody is administered in a maintenance treatment period (or adjuvant phase). In some embodiments, the induction treatment period is followed by the maintenance treatment period. In some embodiments, the induction treatment period is followed by surgical removal of a tumor, which is then followed by the maintenance treatment period. In some embodiments, the dose of anti-PD-1 antibody is different between the maintenance period and the induction period. In some embodiments, the dose of anti-PD-1 antibody in the induction (neoadjuvant) period is 200 mg and the dose in the maintenance (adjuvant) period is 400 mg. In some embodiments, the induction (neoadjuvant) treatment period comprises administering an anti-PD-1 antibody once every 3 weeks. In some embodiments, the induction treatment period comprises three or four three-week cycles. In some embodiments, the maintenance (adjuvant) treatment period comprises administering an anti-PD-1 antibody once every 6 weeks. In some embodiments, the maintenance treatment period comprises one six-week cycle. In some embodiments, the maintenance treatment period comprises two six-week cycles. In some embodiments, the maintenance treatment period comprises three six-week cycles. In some embodiments, the maintenance treatment period comprises four six-week cycles. In some embodiments, the maintenance treatment period comprises five six-week cycles. In some embodiments, the maintenance treatment period comprises six six-week cycles. In some embodiments, the maintenance treatment period comprises seven six-week cycles. In some embodiments, the maintenance treatment period comprises eight six-week cycles. In some embodiments, the maintenance treatment period comprises nine six-week cycles. In some embodiments, the maintenance treatment period comprises ten six-week cycles.

**[00127]** In some embodiments, the anti-PD-1 antibody is administered intravenously at a fixed dose of 200 mg. In some embodiments, the anti-PD-1 antibody is administered intravenously at a

fixed dose of 200 mg once every three-weeks. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered intravenously at a fixed dose of 200 mg. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered intravenously at a fixed dose of 200 mg once every three-weeks. In some embodiments, the IV administration is by IV infusion.

[00128] In some embodiments, the anti-PD-1 antibody is administered intravenously at a dose of 2 mg/kg to 5 mg/kg (*e.g.*, 2 mg/kg or 5 mg/kg). In some embodiments, the anti-PD-1 antibody is administered intravenously at a dose of 2 mg/kg to 5 mg/kg (*e.g.*, 2 mg/kg or 5 mg/kg) once every three-weeks. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered intravenously at a dose of 2 mg/kg to 5 mg/kg (*e.g.*, 2 mg/kg or 5 mg/kg). In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered intravenously at a dose of 2 mg/kg to 5 mg/kg (*e.g.*, 2 mg/kg or 5 mg/kg) every three-weeks. In some embodiments, the IV administration is by IV infusion.

[00129] In some embodiments, the anti-PD-1 antibody is administered intravenously at a fixed dose of 400 mg. In some embodiments, the anti-PD-1 antibody is administered intravenously at a fixed dose of 400 mg once every three-weeks. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered intravenously at a fixed dose of 400 mg. In some embodiments, an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab) is administered intravenously at a fixed dose of 400 mg once every three-weeks. In some embodiments, the IV administration is by IV infusion.

[00130] In some embodiments, an anti-PD-1 antibody (*e.g.*, Tislelizumab) is administered at 200 mg in a neoadjuvant phase, and administered at 400 mg in an adjuvant phase. In some embodiments, the cancer being treated is resected or removed (completely or partially) between



the neoadjuvant treatment phase and the adjuvant treatment phase.

[00131] In some embodiments, the dosage and treatment regimens described herein are for administration to human subjects.

[00132] In another aspect, the present disclosure relates to a method of treating a cancer in a subject in need thereof, wherein: the cancer is a solid cancer, and the solid cancer is selected from the group consisting of a lung cancer, a breast cancer, and a colon cancer, the method comprises parenterally administering to the subject a dose of an anti-PD-1 antibody (*e.g.*, Tislelizumab), or an antigen-binding fragment thereof, wherein the dose is:

(i) about 50 to 800 mg, or (ii) about 2 mg/kg to about 5 mg/kg;

and the anti-PD-1 antibody comprises:

(a) a VH CDR1, VH CDR2, and a VH CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:31, 32 and 33, and

(b) a VL CDR1, VL CDR2, and a VL CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:34, 35 and 36.

[00133] In another aspect the present disclosure relates to a method of treating a cancer in a subject in need thereof, wherein the cancer is a solid cancer, comprising parenterally administering to the subject an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the anti-PD-1 antibody is administered:

(i) at a dose from about 50 to 800 mg, or (ii) at a dose from about 2 mg/kg to about 5 mg/kg;

and the anti-PD-1 antibody comprises:

(a) a VH CDR1, VH CDR2, and a VH CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:31, 32 and 33, and

(b) a VL CDR1, VL CDR2, and a VL CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:34, 35 and 36; and the method further comprises administering a therapeutically effective amount of chemotherapeutic drugs comprising (i) a platinum chemotherapy drug, or (ii) carboplatin, and paclitaxel or nab-paclitaxel.

[00134] In some embodiments, the anti-PD-1 antibody is administered at a dose from about 2 mg/kg to 5 mg/kg, optionally wherein the anti-PD-1 antibody is administered at a dose of about 2mg/kg Q3W, 5mg/kg Q3W or 200 mg Q3W, optionally wherein the anti-PD-1 antibody is administered at a dose of about 400 mg, optionally wherein the anti-PD-1 antibody is administered at a dose of about 150 mg Q2W, optionally wherein the anti-PD-1 antibody is administered at a dose of about 300 mg Q4W, and optionally wherein the anti-PD-1 antibody is administered at a dose of about 400 mg Q6W. In some embodiments, the anti-PD-1 antibody is administered at a dose from about 50 to 800 mg, optionally wherein the anti-PD-1 antibody is administered at 100 mg, 150 mg, 200, mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, or 800 mg. In some embodiments, the PD-1 antibody is administered every week, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, or every 6 weeks, optionally wherein the anti-PD-1 antibody is administered at 150 mg every two weeks, 300 mg every four weeks, or 400 mg every six weeks. In some embodiments, the PD-1 antibody is administered at a first dose prior to surgical removal of the solid cancer, and wherein the PD-1 antibody is administered at a second dose after surgical removal of the solid cancer. In some embodiments, the first dose is:

about 50 to 800 mg, optionally wherein the anti-PD-1 antibody is administered at 100 mg, 150 mg, 200, mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, or 800 mg, or

about 2 mg/kg to about 5 mg/kg; optionally wherein the first dose is 200 mg once every three-weeks (Q3W);

and wherein the second dose is:

about 50 to 800 mg, optionally wherein the anti-PD-1 antibody is administered at 100 mg, 150 mg, 200, mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, or 800 mg, or

about 2 mg/kg to about 5 mg/kg; optionally wherein the first dose is 400 mg once every six weeks (Q6W).

(c) Anti-Cancer Agents/Chemotherapeutic Drugs

[00135] In some embodiments, a subject described herein is administered an anti-cancer agent. The term “anti-cancer agent” as used herein refers to any agent that can be used to treat a cell proliferative disorder such as cancer, including but not limited to, cytotoxic agents, chemotherapeutic agents, radiotherapy and radiotherapeutic agents, targeted anti-cancer agents, and immunotherapeutic agents, including cellular therapies.

[00136] In some embodiments, the anti-PD-1 antibodies and antigen-binding fragments of the present disclosure are used in combination with one or more anti-cancer agents. In some embodiments, a subject described herein is administered an anti-PD-1 antibody and further administered an anti-cancer agent described herein.

[00137] In some embodiments, the anti-PD-1 antibodies of the present disclosure are used in combination with one or more chemotherapeutic agents or drugs (*e.g.*, one, two or three chemotherapeutic agents or drugs). In some embodiments, the treatment methods described herein comprise administration to a subject (*e.g.*, a human) of an anti-PD-1 antibody of the present disclosure and one or more chemotherapeutic drugs (*e.g.*, one, two or three chemotherapeutic drugs).

[00138] Classes of chemotherapeutic agents that can be used include, but are not limited to: microtubule inhibitors, *e.g.*, taxanes (paclitaxel, docetaxel), and vinca alkaloids (vincristine, vinblastine, vinorelbine); antimetabolites (5-fluorouracil, capecitabine, gemcitabine), and antifolates (methotrexate, pemetrexed); kinase inhibitors (crizotinib, erlotinib, sunitinib); topoisomerase inhibitors (deruxtecan, topotecan, irinotecan, anthracyclines, etoposide); cell-cycle independent drugs, *e.g.*, platinum compounds and analogues (oxaliplatin), triazenes, alkylating agents (cyclophosphamide), spindle poison plant alkaloids (doxorubicin), cytotoxic/antitumor antibiotics (bleomycin, mithramycin, mitomycin), photosensitizers, anti-estrogens and selective estrogen receptor modulators (SERMs), anti-progesterones, estrogen receptor down-regulators (ERDs), estrogen receptor antagonists, luteinizing hormone-releasing hormone agonists, anti-androgens, aromatase inhibitors, EGFR inhibitors, VEGF inhibitors, and anti-sense oligonucleotides that inhibit expression of genes implicated in abnormal cell proliferation or tumor growth. Current standard of care (SOC) treatments for certain cancers, in the early-line setting include chemotherapy based on fluoropyrimidine, oxaliplatin, and

irinotecan used in combination or sequentially, with option for monoclonal antibodies targeting vascular endothelial growth factor (VEGF) (*e.g.*, bevacizumab, ziv-aflibercept) or its receptors (*e.g.*, ramucirumab), and in patients with Ras wild type tumors, monoclonal antibodies targeting the epidermal growth factor (EGF) receptor (*e.g.*, cetuximab, panitumumab). Treatment options for heavily pre-treated patients beyond the second-line setting are especially limited and associated toxicities can be severe.

[00139] In some embodiments, the chemotherapeutic agent is selected from one or more of the following: paclitaxel or a paclitaxel agent; (*e.g.*, Abraxane®), docetaxel; carboplatin; topotecan; deruxtecan; cisplatin; 5-fluorouracil, irinotecan, doxorubicin, lenalidomide, 5-azacytidine, ifosfamide, oxaliplatin, pemetrexed disodium, cyclophosphamide, etoposide, decitabine, fludarabine, vincristine, bendamustine, chlorambucil, busulfan, gemcitabine, melphalan, pentostatin, mitoxantrone, and pemetrexed disodium.

[00140] In some embodiments, the chemotherapeutic drug is a platinum chemotherapy.

[00141] In some embodiments, the chemotherapeutic drug is cisplatin.

[00142] In some embodiments, the chemotherapeutic drug is carboplatin.

[00143] In some embodiments, the treatment methods described herein comprise administration to a subject (*e.g.*, a human) of an anti-PD-1 antibody of the present disclosure and either cisplatin or carboplatin. In some embodiments, it is in physician's discretion whether to administer cisplatin or carboplatin.

[00144] In some embodiments, the chemotherapeutic drug is pemetrexed. In some embodiments, the treatment methods described herein comprise administration to a subject (*e.g.*, a human) of an anti-PD-1 antibody of the present disclosure and pemetrexed.

[00145] In some embodiments, the chemotherapeutic drug is paclitaxel. In some embodiments, the treatment methods described herein comprise administration to a subject (*e.g.*, a human) of an anti-PD-1 antibody of the present disclosure and paclitaxel.

[00146] In some embodiments, the chemotherapeutic drug is etoposide. In some embodiments, the treatment methods described herein comprise administration to a subject (*e.g.*, a human) of an anti-PD-1 antibody of the present disclosure and etoposide.

[00147] In some embodiments, the treatment methods described herein comprise administration to a subject (*e.g.*, a human) of (i) an anti-PD-1 antibody of the present disclosure, (ii) either cisplatin or carboplatin, and (iii) pemetrexed or paclitaxel.

[00148] In some embodiments, the chemotherapeutic agent is 5-fluorouracil. In some embodiments, the treatment methods described herein comprise administration to a subject (*e.g.*, a human) of (i) an anti-PD-1 antibody of the present disclosure, (ii) 5-fluorouracil, and (iii) cisplatin.

[00149] The dosing of the chemotherapy drugs can be any dosing known in the art (*e.g.*, any dose and administration regimen known in the art to be effective) or any dosing described herein.

*A. Cisplatin*

[00150] In some embodiments, a patient described herein is administered Cisplatin in combination with an anti-PD-1 antibody described herein. In some embodiments, a patient is administered Cisplatin in combination with Tislelizumab. In some embodiments, a patient is administered Cisplatin in combination with an anti-PD-1 antibody described herein and either pemetrexed or paclitaxel. In some embodiments, a patient is administered Cisplatin in combination with Tislelizumab and one or both of pemetrexed and paclitaxel. In some embodiments, a patient is administered Cisplatin in combination with Tislelizumab and 5-fluorouracil.

[00151] In some embodiments, Cisplatin is administered parenterally. In some embodiments, Cisplatin is administered at a dose of about 20 mg/m<sup>2</sup> to about 100 mg/m<sup>2</sup>. In some embodiments, Cisplatin is administered at about 20 mg/m<sup>2</sup>, 25 mg/m<sup>2</sup>, 30 mg/m<sup>2</sup>, 35 mg/m<sup>2</sup>, 40 mg/m<sup>2</sup>, 45 mg/m<sup>2</sup>, 50 mg/m<sup>2</sup>, 55 mg/m<sup>2</sup>, 60 mg/m<sup>2</sup>, 65 mg/m<sup>2</sup>, 70 mg/m<sup>2</sup>, 75 mg/m<sup>2</sup>, 80 mg/m<sup>2</sup>, 85 mg/m<sup>2</sup>, 90 mg/m<sup>2</sup>, 95 mg/m<sup>2</sup>, or 100 mg/m<sup>2</sup> (or any value in between of these values). In some embodiments, Cisplatin is administered at about 75 mg/m<sup>2</sup>. In some embodiments, Cisplatin is administered at 75 mg/m<sup>2</sup>.

[00152] In some embodiments, Cisplatin is administered intravenously. In some embodiments, Cisplatin is administered as an intravenous infusion over at least 2 hours. In some embodiments, Cisplatin is administered as an intravenous infusion over 2 hours. In some

embodiments, Cisplatin is administered once every week. In some embodiments, Cisplatin is administered once every 3 weeks. In some embodiments, Cisplatin is administered on Day 1 once every 3 weeks. In some embodiments, Cisplatin is administered on Day 2 once every 3 weeks. In some embodiments, Cisplatin is administered on Days 1-3 every 3 weeks. In some embodiments, Cisplatin is administered on Days 1-5 every 3 weeks.

[00153] In some embodiments, Cisplatin is administered for 1 cycle. In some embodiments, Cisplatin is administered for 2 cycles. In some embodiments, Cisplatin is administered for 3 cycles. In some embodiments, Cisplatin is administered for 4 cycles. In some embodiments, a cycle is 3 weeks.

[00154] In some embodiments, Cisplatin is administered for 4 three-week cycles.

[00155] In some embodiments, Cisplatin is administered on Day 1 of each cycle. In some embodiments, Cisplatin is administered on Day 2 of each cycle. In some embodiments, Cisplatin is administered on Day 3 of each cycle. In some embodiments, Cisplatin is administered on Day 4 of each cycle. In some embodiments, Cisplatin is administered on Day 5 of each cycle.

[00156] In some embodiments, the methods described herein comprise administration of Cisplatin once every cycle, wherein each cycle is three-weeks, on Day 1 of each cycle for 4 cycles.

[00157] In some embodiments, the methods described herein comprise intravenous administration of 75 mg/m<sup>2</sup> Cisplatin on Day 1 of each 21 days cycle (and optionally wherein Cisplatin is infused over 2 hours), and optionally the administration is for 4 cycles or more.

#### *B. Carboplatin*

[00158] In some embodiments, a patient described herein is administered Carboplatin in combination with an anti-PD-1 antibody described herein. In some embodiments, a patient is administered Carboplatin in combination with Tislelizumab. In some embodiments, a patient is administered Carboplatin in combination with an anti-PD-1 antibody described herein and either pemetrexed or paclitaxel. In some embodiments, a patient is administered Carboplatin in combination with Tislelizumab and one or both of pemetrexed and paclitaxel.

[00159] In some embodiments, Carboplatin is administered parenterally. In some

embodiments, Carboplatin is administered as a target of AUC 4 mg/mL/min to 6 mg/mL/min (and any value in between, *e.g.*, 5 to 6 mg/mL/min). In some embodiments, Carboplatin is administered as a target of AUC 4 mg/mL/min. In some embodiments, Carboplatin is administered as a target of AUC 5 mg/mL/min. In some embodiments, Carboplatin is administered as a target of AUC 6 mg/mL/min. As used herein the term “Area under the Curve” or “AUC” defines the dose of carboplatin administered to a subject. The AUC is area under the plasma concentration-time curve. In some embodiments, a subject is administered carboplatin to achieve the above-noted AUC, *e.g.*, AUC of 5 mg/mL/min. In some embodiments, the dosing of carboplatin is calculated according to Calvert formula dosing. A skilled artisan can calculate the amount of carboplatin necessary to achieve a given AUC in a subject. See Calvert et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *Journal of Clinical Oncology*, 1989, 7(11): 1748-56, the contents of which are incorporated by reference herein in its entirety.

**[00160]** In some embodiments, Carboplatin is administered intravenously. In some embodiments, Carboplatin is administered as an intravenous infusion over 15 to 60 minutes (or any value in between). In some embodiments, Carboplatin is administered as an intravenous infusion 15 minutes. In some embodiments, Carboplatin is administered as an intravenous infusion 30 minutes. In some embodiments, Carboplatin is administered as an intravenous infusion 45 minutes. In some embodiments, Carboplatin is administered as an intravenous infusion 60 minutes.

**[00161]** In some embodiments, Carboplatin is administered once every week. In some embodiments, Carboplatin is administered once every 3 weeks. In some embodiments, Carboplatin is administered on Day 1 once every 3 weeks.

**[00162]** In some embodiments, Carboplatin is administered for 1 cycle. In some embodiments, Carboplatin is administered for 2 cycles. In some embodiments, Carboplatin is administered for 3 cycles. In some embodiments, Carboplatin is administered for 4 cycles. In some embodiments, a cycle is 3 weeks.

**[00163]** In some embodiments, Carboplatin is administered for 4 three-week cycles. In some embodiments, Carboplatin is administered on Day 1 of each cycle.

[00164] In some embodiments, the methods described herein comprise administration of Carboplatin once every cycle, wherein each cycle is three-weeks, on Day 1 of each cycle for 4 cycles.

[00165] In some embodiments, the methods described herein comprise intravenous administration of AUC5 Carboplatin on Day 1 of each 21 days cycle (and optionally wherein Carboplatin is infused over 15 to 60 minutes), and optionally the administration is for 4 cycles or more. In some embodiments, carboplatin is administered to achieve AUC of 5 mg/mL/min in accordance with Calvert formula dosing (*e.g.*, as described herein).

*C. Pemetrexed*

[00166] In some embodiments, a patient described herein is administered pemetrexed in combination with an anti-PD-1 antibody described herein. In some embodiments, a patient is administered pemetrexed in combination with Tislelizumab. In some embodiments, a patient is administered a combination of the anti-PD-1 antibody described herein, Carboplatin or Cisplatin, and pemetrexed. In some embodiments, a patient is administered a combination of Tislelizumab, Carboplatin or Cisplatin, and pemetrexed. In some of these embodiments, the cancer is a non-squamous cell carcinoma (*e.g.*, non-squamous cell NSCLC).

[00167] In some embodiments, pemetrexed is administered parenterally. In some embodiments, pemetrexed is administered at a dose of about 250 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup> (or any value in between). In some embodiments, pemetrexed is administered at about 500 mg/m<sup>2</sup>. In some embodiments, pemetrexed is administered at 500 mg/m<sup>2</sup>.

[00168] In some embodiments, pemetrexed is administered intravenously. In some embodiments, pemetrexed is administered as an intravenous infusion over about 10 minutes or at least 10 minutes. In some embodiments, pemetrexed is administered as an intravenous infusion over 10 minutes.

[00169] In some embodiments, pemetrexed is administered once every three weeks. In some embodiments, pemetrexed is administered on Day 1 of a 3-week (21 day) cycle. In some embodiments, pemetrexed is administered on Day 2 of a 3-week (21 day) cycle. In some embodiments, pemetrexed is administered on Day 3 of a 3-week (21 day) cycle. In some



embodiments, pemetrexed is administered on Day 4 of a 3-week (21 day) cycle. In some embodiments, pemetrexed is administered on Day 5 of a 3-week (21 day) cycle. In some embodiments, pemetrexed is administered on Days 1-3 every 3 weeks. In some embodiments, pemetrexed is administered on Days 1-5 every 3 weeks.

[00170] In some embodiments, pemetrexed is administered for 1 cycle. In some embodiments, pemetrexed is administered for 2 cycles. In some embodiments, pemetrexed is administered for 3 cycles. In some embodiments, pemetrexed is administered for 4 cycles. In some embodiments, a cycle is 3 weeks.

[00171] In some embodiments, pemetrexed is administered for 4 three-week cycles.

[00172] In some embodiments, pemetrexed is administered on Day 1 of each cycle.

[00173] In some embodiments, the methods described herein comprise administration of pemetrexed once every cycle, wherein each cycle is three-weeks, for 3 or 4 cycles.

[00174] In some embodiments, the methods described herein comprise intravenous administration of 500 mg/m<sup>2</sup> pemetrexed on Day 1 of each 21 days cycle (and optionally wherein pemetrexed is infused over 10 minutes), and optionally the administration is for 3, 4 cycles or more.

#### *D. Paclitaxel*

[00175] In some embodiments, a patient described herein is administered paclitaxel in combination with an anti-PD-1 antibody described herein. In some embodiments, a patient is administered paclitaxel in combination with Tislelizumab. In some embodiments, a patient is administered a combination of the anti-PD-1 antibody described herein, Carboplatin or Cisplatin, and paclitaxel. In some embodiments, a patient is administered a combination of Tislelizumab, Carboplatin or Cisplatin, and paclitaxel. In some of these embodiments, the cancer is a squamous cell carcinoma (*e.g.*, squamous cell NSCLC).

[00176] In some embodiments, paclitaxel is administered parenterally. In some embodiments, paclitaxel is administered at a dose of about 80 mg/m<sup>2</sup> to about 400 mg/m<sup>2</sup> (or any value in between). In some embodiments, paclitaxel is administered at about 175 mg/m<sup>2</sup>. In some embodiments, paclitaxel is administered at 175 mg/m<sup>2</sup>.

[00177] In some embodiments, paclitaxel is administered intravenously. In some embodiments, paclitaxel is administered as an intravenous infusion over about 3 hours or at least 3 hours. In some embodiments, paclitaxel is administered as an intravenous infusion over 3 hours.

[00178] In some embodiments, paclitaxel is administered once every three weeks. In some embodiments, paclitaxel is administered on Day 1 of a 3-week (21 day) cycle. In some embodiments, paclitaxel is administered on Day 2 of a 3-week (21 day) cycle. In some embodiments, paclitaxel is administered on Day 3 of a 3-week (21 day) cycle. In some embodiments, paclitaxel is administered on Day 4 of a 3-week (21 day) cycle. In some embodiments, paclitaxel is administered on Day 5 of a 3-week (21 day) cycle. In some embodiments, paclitaxel is administered on Days 1-3 every 3 weeks. In some embodiments, paclitaxel is administered on Days 1-5 every 3 weeks.

[00179] In some embodiments, paclitaxel is administered for 1 cycle. In some embodiments, paclitaxel is administered for 2 cycles. In some embodiments, paclitaxel is administered for 3 cycles. In some embodiments, paclitaxel is administered for 4 cycles. In some embodiments, a cycle is 3 weeks.

[00180] In some embodiments, paclitaxel is administered for 4 three-week cycles.

[00181] In some embodiments, paclitaxel is administered on Day 1 of each cycle.

[00182] In some embodiments, the methods described herein comprise administration of paclitaxel once every cycle, wherein each cycle is three-weeks, for 3 or 4 cycles. In some embodiments, the methods described herein comprise intravenous administration of  $175 \text{ mg/m}^2$  paclitaxel on Day 1 of each 21 days cycle (and optionally wherein paclitaxel is infused over 3 hours), and optionally the administration is for 3, 4 cycles or more.

*E. Etoposide*

[00183] In some embodiments, a patient described herein is administered Etoposide in combination with an anti-PD-1 antibody described herein. In some embodiments, a patient is administered Etoposide in combination with Tislelizumab. In some embodiments, a patient is administered a combination of the anti-PD-1 antibody described herein, Carboplatin or Cisplatin,

and Etoposide. In some embodiments, a patient is administered a combination of Tislelizumab, Carboplatin or Cisplatin, and Etoposide.

**[00184]** In some embodiments, Etoposide is administered parenterally. In some embodiments, Etoposide is administered at a dose of about 80 mg/m<sup>2</sup> to about 140 mg/m<sup>2</sup> (or any value in between). In some embodiments, Etoposide is administered at 80 mg/m<sup>2</sup>. In some embodiments, Etoposide is administered at 90 mg/m<sup>2</sup>. In some embodiments, Etoposide is administered at 100 mg/m<sup>2</sup>. In some embodiments, Etoposide is administered at 110 mg/m<sup>2</sup>. In some embodiments, Etoposide is administered at 120 mg/m<sup>2</sup>. In some embodiments, Etoposide is administered at 130 mg/m<sup>2</sup>. In some embodiments, Etoposide is administered at 140 mg/m<sup>2</sup>.

**[00185]** In some embodiments, Etoposide is administered intravenously. In some embodiments, Etoposide is administered as an intravenous infusion over at least 60 minutes. In some embodiments, Etoposide is administered as an intravenous infusion over 60 minutes.

**[00186]** In some embodiments, Etoposide is administered once every week. In some embodiments, Etoposide is administered three times in three-weeks. In some embodiments, Etoposide is administered 3 times in the first week of a 3-week (21 day) cycle. In some embodiments, Etoposide is administered on Day 1 of a 3-week (21 day) cycle. In some embodiments, Etoposide is administered on Day 2 of a 3-week (21 day) cycle. In some embodiments, Etoposide is administered on Day 3 of a 3-week (21 day) cycle. In some embodiments, Etoposide is administered on Day 4 of a 3-week (21 day) cycle. In some embodiments, Etoposide is administered on Day 5 of a 3-week (21 day) cycle. In some embodiments, Etoposide is administered on Days 1-3 every 3 weeks. In some embodiments, Etoposide is administered on Days 1-5 every 3 weeks.

**[00187]** In some embodiments, Etoposide is administered for 1 cycle. In some embodiments, Etoposide is administered for 2 cycles. In some embodiments, Etoposide is administered for 3 cycles. In some embodiments, Etoposide is administered for 4 cycles. In some embodiments, a cycle is 3 weeks.

**[00188]** In some embodiments, Etoposide is administered for 4 three-week cycles.

**[00189]** In some embodiments, Etoposide is administered on Day 1, Day 2 and Day 3 of each

cycle. In some embodiments, Etoposide is administered on Day 1, Day 2, Day 3, Day 4 and Day 5 of each cycle.

[00190] In some embodiments, the methods described herein comprise administration of Etoposide three times every cycle, wherein each cycle is three-weeks, for 4 cycles.

[00191] In some embodiments, the methods described herein comprise intravenous administration of 100 mg/m<sup>2</sup> Etoposide on Day 1 to Day 3 of each 21 days cycle (and optionally wherein Etoposide is infused over 60 minutes), and optionally the administration is for 4 cycles or more.

*F. 5-fluorouracil*

[00192] In some embodiments, a patient described herein is administered 5-fluorouracil in combination with an anti-PD-1 antibody described herein. In some embodiments, a patient is administered 5-fluorouracil in combination with Tislelizumab. In some embodiments, a patient is administered 5-fluorouracil in combination with an anti-PD-1 antibody described herein and cisplatin. In some embodiments, a patient is administered Cisplatin in combination with Tislelizumab and 5-fluorouracil.

[00193] In some embodiments, 5-fluorouracil is administered intravenously. In some embodiments, 5-fluorouracil is administered at a dose of about 200 mg/m<sup>2</sup> to about 3000 mg/m<sup>2</sup>. In some embodiments, 5-fluorouracil is administered at about 200 mg/m<sup>2</sup>, 300 mg/m<sup>2</sup>, 400 mg/m<sup>2</sup>, 500 mg/m<sup>2</sup>, 600 mg/m<sup>2</sup>, 700 mg/m<sup>2</sup>, 800 mg/m<sup>2</sup>, 900 mg/m<sup>2</sup>, 1000 mg/m<sup>2</sup>, 1200 mg/m<sup>2</sup>, 1500 mg/m<sup>2</sup>, 1700 mg/m<sup>2</sup>, 2000 mg/m<sup>2</sup>, 2200 mg/m<sup>2</sup>, 2500 mg/m<sup>2</sup>, 2700 mg/m<sup>2</sup>, or 3000 mg/m<sup>2</sup> (or any value in between of these values).

[00194] In some embodiments, 5-fluorouracil is administered intravenously. In some embodiments, 5-fluorouracil is administered as an intravenous bolus. In some embodiments, 5-fluorouracil is administered as an intravenous infusion. In some embodiments, 5-fluorouracil is administered as an intravenous infusion over 24 hours. In some embodiments, 5-fluorouracil is administered as an intravenous infusion over 46 hours. In some embodiments, 5-fluorouracil is administered every week. In some embodiments, 5-fluorouracil is administered every two weeks. In some embodiments, 5-fluorouracil is administered every week for two weeks and then is

administered again after three weeks.

[00195] In some embodiments, 5-fluorouracil is administered for 1 cycle. In some embodiments, 5-fluorouracil is administered for 2 cycles. In some embodiments, 5-fluorouracil is administered for 4 cycles. In some embodiments, 5-fluorouracil is administered for 6 cycles. In some embodiments, 5-fluorouracil is administered for 8 cycles.

[00196] In some embodiments, 5-fluorouracil is administered at 400 mg/m<sup>2</sup> by intravenous bolus on Day 1 of a treatment cycle, followed by 2400 mg/m<sup>2</sup> to 3000 mg/m<sup>2</sup> intravenously as a continuous infusion over 46 hours every two weeks. In some embodiments, 5-fluorouracil is administered at 500 mg/m<sup>2</sup> by intravenous bolus on Days 1, 8, 15, 22, 29, and 36 of a treatment cycle in 8-week cycles. In some embodiments, 5-fluorouracil is administered at 500 mg/m<sup>2</sup> or 600 mg/m<sup>2</sup> intravenously on Days 1 and 8 of a treatment cycle every 28 days for 6 cycles. In some embodiments, 5-fluorouracil is administered at 200 mg/m<sup>2</sup> to 1000 mg/m<sup>2</sup> intravenously as a continuous infusion over 24 hours. In some embodiments, 5-fluorouracil is administered at 400 mg/m<sup>2</sup> by intravenous bolus on Day 1 of a treatment cycle followed by 2400 mg/m<sup>2</sup> intravenously as a continuous infusion over 46 hours every two weeks.

#### G. Radiotherapy

[00197] In some embodiments, a patient described herein is administered radiotherapy in combination with an anti-PD-1 antibody described herein. In some embodiments, a patient is administered radiotherapy in combination with Tislelizumab. In some embodiments, a patient is administered radiotherapy in combination with an anti-PD-1 antibody described herein and one or both of cisplatin and paclitaxel or cisplatin and 5-fluorouracil. In some embodiments, a patient is administered radiotherapy in combination with Tislelizumab and one or both of cisplatin and paclitaxel or cisplatin and 5-fluorouracil.

[00198] In some embodiments, radiotherapy is administered at about 10 gray to about 80 gray. In some embodiments, radiotherapy is administered at about 10 gray. In some embodiments, radiotherapy is administered at about 20 gray. In some embodiments, radiotherapy is administered at about 30 gray. In some embodiments, radiotherapy is administered at about 40 gray. In some embodiments, radiotherapy is administered at about 50 gray. In some

embodiments, radiotherapy is administered at about 60 gray. In some embodiments, radiotherapy is administered at about 70 gray. In some embodiments, radiotherapy is administered at about 80 gray.

[00199] In some embodiments, radiotherapy is administered over about 5 fractions. In some embodiments, radiotherapy is administered over about 10 fractions. In some embodiments, radiotherapy is administered over about 15 fractions. In some embodiments, radiotherapy is administered over about 20 fractions. In some embodiments, radiotherapy is administered over about 25 fractions. In some embodiments, radiotherapy is administered over about 30 fractions. In some embodiments, radiotherapy is administered over about 35 fractions. In some embodiments, radiotherapy is administered over about 40 fractions.

[00200] In some embodiments, radiotherapy is administered at 40 gray/20 fractions.

(d) Combination Therapies

[00201] The combination therapy may be administered as a simultaneous, or separate or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. The combined administration includes co-administration, using separate formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or each of) active agents simultaneously exert their biological activities.

[00202] In some embodiments, the combination therapies provided herein provide a synergistic and/or statistically improved effect relative to either therapy when used as a single agent. For example, the combination therapies disclosed herein result in significant improvement in patient outcome in early-stage NSCLC or mid-stage NSCLC. For example, the combination therapies, in some embodiments, prolong patient survival and progression-free survival while having a manageable toxicity profile in patients suffering from early-stage NSCLC or mid-stage NSCLC.

[00203] Suitable dosages for any of the above co-administered agents are those presently used and may be lowered due to the combined action (synergy), such as to increase the therapeutic index or mitigate toxicity or other side-effects or consequences.

[00204] In some embodiments, the anti-PD-1 antibody and one or more chemotherapy drug (or combination treatment regimens described herein) may be further combined with any other therapy. In some embodiments, the anti-PD-1 antibody and one or more chemotherapy drug (or combination treatment regimens described herein) may be further combined with any therapy except any one or more therapies listed in the exclusion criteria described in the example section of this application. In some embodiments, the anti-PD-1 antibody and one or more chemotherapy drug (or combination treatment regimens described herein) may be further combined with, *e.g.*, radiotherapy. In some embodiments, the anti-PD-1 antibody and one or more chemotherapy drug (or combination treatment regimens described herein) may be further combined with, *e.g.*, a steroid or hormone therapy, optionally wherein the steroid or hormone therapy is administered to alleviate incidence of immune-mediated adverse events.

[00205] In some embodiments, the combination therapy is any combination therapy described herein, including without limitation the combination therapies, dosing, duration and regimens described in the example section of this application.

[00206] In some embodiments, the combination therapy described herein can be combined with additional therapies consistent with the inclusion criteria described in the example section of this application.

[00207] In some embodiments, the combination therapy described herein can be combined with additional therapies consistent with the exclusion criteria described in the example section of this application (*i.e.*, wherein the therapies listed in the exclusion criteria are excluded or not selected for the combination).

[00208] In some embodiments, the additional therapy can be one or more of the following: tyrosine kinase inhibitor (*e.g.*, EGFR inhibitor (*e.g.*, erlotinib), multikinase inhibitor (*e.g.*, MGCD265, RGB-286638), CD-20 targeting agent (*e.g.*, rituximab, ofatumumab, RO5072759, LFB-R603), CD52 targeting agent (*e.g.*, alemtuzumab), prednisolone, darbepoetin alfa, lenalidomide, Bcl-2 inhibitor (*e.g.*, oblimersen sodium), aurora kinase inhibitor (*e.g.*, MLN8237, TAK-901), proteasome inhibitor (*e.g.*, bortezomib), CD-19 targeting agent (*e.g.*, MEDI-551, MOR208), MEK inhibitor (*e.g.*, ABT-348), JAK-2 inhibitor (*e.g.*, INCB018424), mTOR inhibitor (*e.g.*, temsirolimus, everolimus), BCR/ABL inhibitor (*e.g.*, imatinib), ET-A receptor

antagonist (*e.g.*, ZD4054), TRAIL receptor 2 (TR-2) agonist (*e.g.*, CS-1008), EGEN-001, Polo-like kinase 1 inhibitor (*e.g.*, BI 672).

**[00209]** In some embodiments, the additional therapy is a radiotherapy. In some embodiments, radiotherapy is administered after surgical resecting or removal of the tumor or cancerous tissue. In some embodiments, radiotherapy is administered before maintenance or adjuvant treatment period with an anti-PD-1 antibody (*e.g.*, at 400 mg dose). In some embodiments, radiotherapy is administered 30 to 60 days (*e.g.*, 30, 40, 50 or 60 days) after the surgical resecting of the tumor or cancer. In some embodiments, radiotherapy is administered at least 30 days after the surgical resecting of the tumor or cancer. In some embodiments, radiotherapy is administered not more than 60 days after the surgical resecting of the tumor or cancer. In some embodiments, the maintenance or adjuvant treatment period with an anti-PD-1 antibody (*e.g.*, at 400 mg dose) starts between 7 and 30 days (*e.g.*, 7, 14, 21, 28 or 30 days) after the radiotherapy. In some embodiments, the maintenance or adjuvant treatment period with an anti-PD-1 antibody (*e.g.*, at 400 mg dose) starts at least 7 days after the radiotherapy. In some embodiments, the maintenance or adjuvant treatment period with an anti-PD-1 antibody (*e.g.*, at 400 mg dose) starts not more than 30 days after the radiotherapy. In some embodiments, the subject is not treated with radiotherapy. In some embodiments, the surgical resecting is not followed by radiotherapy. In some embodiments, the treatment regimen described herein does not comprise radiotherapy. In some embodiments, the maintenance or adjuvant treatment period with an anti-PD-1 antibody (*e.g.*, at 400 mg dose) starts between 2 and 8 weeks (*e.g.*, 2, 3, 4, 5, 6, 7, or 8 weeks) after the surgical resection of the tumor or cancer. In some embodiments, the maintenance or adjuvant treatment period with an anti-PD-1 antibody (*e.g.*, at 400 mg dose) starts at least 2 weeks after the surgical resection of the tumor or cancer. In some embodiments, the maintenance or adjuvant treatment period with an anti-PD-1 antibody (*e.g.*, at 400 mg dose) starts not more than 8 weeks after the surgical resection of the tumor or cancer.

**[00210]** In some embodiments, the additional therapy can be an antibody binding to another immune checkpoint molecule.

**[00211]** In some embodiments, the amounts of the anti-PD-1 antibody disclosed herein and the one or chemotherapy drugs, as well as their relative timings of administration, be determined



by the individual needs of the patient to be treated, administration route, severity of disease or illness, dosing schedule, as well as evaluation and judgment of the designated doctor.

[00212] In some embodiments, the anti-PD-1 antibody is administered before (*e.g.*, 60 minutes or more before) administration of one or more chemotherapy drugs. In some embodiments, the anti-PD-1 antibody is administered before (*e.g.*, 30 minutes or more before) administration of one or more chemotherapy drugs. In some embodiments, the anti-PD-1 antibody is administered 60 minutes or more before administration of one or more chemotherapy drugs in cycle 1 and optionally cycle 2. In some embodiments, the anti-PD-1 antibody is administered 30 minutes or more before administration of one or more chemotherapy drugs in cycle 3, cycle 4, and/or any cycle subsequent to cycle 3.

[00213] In some embodiments, the dosing, frequency and/or duration of administration of the anti-PD-1 antibody and one or more chemotherapeutic agents is as described herein.

[00214] In some embodiments, the anti-PD-1 antibody and the one or more chemotherapeutic drugs described herein are administered on the same day. In some embodiments, the anti-PD-1 antibody and the one or more chemotherapeutic drugs described herein are administered at least 30 minutes apart from each other. In some embodiments, the anti-PD-1 antibody and the one or more chemotherapeutic drugs described herein are administered in any sequence. In some embodiments, the anti-PD-1 antibody is administered before the administration of the one or more chemotherapeutic drugs as described herein (*e.g.*, at least 30 minutes before).

[00215] In some embodiments, anti-PD-1 antibody (such as an anti-PD-1 antibody comprising the CDRs of the 317-4B6 antibody described herein, the Vh of SEQ ID NO:24, and/or the Vl of SEQ ID NO:26 (*e.g.*, Tislelizumab)) is administered intravenously at a dose of 200 mg on Day 1 of each 21 cycle; cisplatin or carboplatin is administered intravenously on Day 1 of each 21 day cycle; and pemetrexed or paclitaxel is administered intravenously on Day 1 of each 21 day cycle. In some of these embodiments, cisplatin is administered IV at 75 mg/m<sup>2</sup> (and optionally infused over 2 hours) or carboplatin is administered IV at AUC5 (and optionally infused over 15-60 minutes to achieve an AUC of 5 mg/mL/min). In some of these embodiments, pemetrexed is administered IV at 500 mg/m<sup>2</sup> (and optionally infused over 10 minutes) or paclitaxel is administered IV at 175 mg/m<sup>2</sup> (and optionally infused over 3 hours). In some of these

embodiments, in cycle 1, the anti-PD-1 antibody is administered 60 minutes or more before administration of cisplatin, carboplatin, pemetrexed and/or paclitaxel (and optionally the anti-PD-1 antibody is infused over 60 minutes). In some of these embodiments, in cycle 2, the anti-PD-1 antibody is administered 60 minutes or more before administration of cisplatin, carboplatin, pemetrexed and/or paclitaxel (and optionally the anti-PD-1 antibody is infused over 30 minutes). In some of these embodiments, in cycles 3 and 4, the anti-PD-1 antibody is administered 30 minutes or more (*e.g.*, less than 60 minutes) before administration of cisplatin, carboplatin, pemetrexed and/or paclitaxel (and optionally the anti-PD-1 antibody is infused over 30 minutes). In some of these embodiments, in subsequent cycles (after cycle 4), the anti-PD-1 antibody is administered alone (without chemotherapy), and optionally the anti-PD-1 antibody is infused over 30 minutes or more (*e.g.*, for less than 60 minutes).

(e) Cancers Treated As Provided Herein

[00216] Treatment regimens for solid cancers (*e.g.*, lung cancer, esophageal cancer) are disclosed herein. In some embodiments, the cancer is non-small cell lung cancer (NSCLC). In some embodiments, the cancer is esophageal cancer.

[00217] In some embodiments, the solid cancer is resectable (surgically removable). In some embodiments, the solid cancer is not locally advanced or metastatic.

[00218] In some embodiments, the solid cancer is stage I. In some embodiments, the solid cancer is stage IIA. In some embodiments, the solid cancer is stage IIB. In some embodiments, the solid cancer is stage IIIA. In some embodiments, the solid cancer is stage IIIB.

[00219] In some embodiments, the cancer is chemotherapy-resistant. In some embodiments, the cancer has progressed after prior chemotherapy.

[00220] In some embodiments, the NSCLC is a squamous cell carcinoma. In some embodiments, the NSCLC is a non-squamous carcinoma. In some embodiments, the NSCLC is an adenocarcinoma. In some embodiments, the NSCLC is a large cell carcinoma. In some such embodiments, the esophageal cancer is an esophageal squamous cell carcinoma. In some such embodiments, the esophageal cancer is an esophageal adenocarcinoma.

[00221] In some embodiments, the NSCLC is resectable. In some embodiments, the NSCLC

is not locally advanced or metastatic. In some embodiments, the esophageal cancer is resectable (e.g., resectable esophageal squamous cell carcinoma). In some embodiments, the esophageal cancer (e.g., esophageal squamous cell carcinoma) is not locally advanced or metastatic.

**[00222]** In some embodiments, the NSCLC is stage I. In some embodiments, the NSCLC is stage IIA. In some embodiments, the NSCLC is stage IIB. In some embodiments, the NSCLC is stage IIIA. In some embodiments, the NSCLC is stage IIIB. In some embodiments, the NSCLC is stage IV. In some embodiments, the cancer is extensive-stage small cell lung cancer (NSCLC). In some embodiments, extensive-stage cancer has spread outside of the lung in which it began or to other parts of the body. In some embodiments, the NSCLC is unresectable. In some embodiments, the NSCLC is locally advanced. In some embodiments, the NSCLC is metastatic. In some embodiments, the esophageal cancer is stage I. In some embodiments, the esophageal cancer is stage IIA. In some embodiments, the esophageal cancer is stage IIB. In some embodiments, the esophageal cancer is stage IIIA. In some embodiments, the esophageal cancer is stage IIIB. In some embodiments, the esophageal cancer is stage IV. In some embodiments, the esophageal cancer is unresectable. In some embodiments, the esophageal cancer is locally advanced. In some embodiments, the esophageal cancer is metastatic.

**[00223]** In some embodiments, the lung cancer is characterized by one or more of liver, lung, lymph node, bone, or adrenal gland metastasis. In some embodiments, the cancer is characterized by liver metastasis. In some embodiments, the cancer is characterized by lung metastasis. In some embodiments, the cancer is characterized by lymph node metastasis. In some embodiments, the cancer is characterized by bone metastasis. In some embodiments, the cancer is characterized by adrenal gland metastasis.

**[00224]** In some embodiments, the cancer (such as lung cancer, *e.g.*, NSCLC) is assessed for expression of immune-mediated biomarkers that are related to response or clinical benefit of the anti-PD-1 antibody, such as tislelizumab, *e.g.*, using tumor biopsy. The biomarker can be, without limitation, PD-L1, TMB, GEP and MSI. Biomarkers expression can be assessed by multiplex immunohistochemistry assay (IHC). The cancer to be treated can be a cancer that has a detectable expression of PD-L1. The cancer to be treated can be a cancer that has a detectable expression of TMB. The cancer to be treated can be a cancer that has a detectable gene

expression profile (GEP), (such as an immune-mediated GEP). The cancer to be treated can be a cancer that has a detectable expression of MSI.

[00225] In some embodiments, the cells of the lung cancer comprise high level of PD-L1 expression as measured by the percentage of PD-L1 positive tumor or immune cells or as measured by the areas occupied by PD-L1 positive tumor and immune cells, divided by the total tumor area. In some embodiments, the subject has a low level of PD-L1 expression as measured by the percentage of PD-L1 positive tumor or immune cells or as measured by the areas occupied by PD-L1 positive tumor and immune cells, divided by the total tumor area. In some embodiments, the subject has less than 1% of PD-L1 expression as measured by PD-L1 positive tumor or immune cells or as measured by the areas occupied by PD-L1 positive tumor and immune cells, divided by the total tumor area. In some embodiments, the subject has equal or more than 1% of PD-L1 expression as measured by PD-L1 positive tumor or immune cells or as measured by the areas occupied by PD-L1 positive tumor and immune cells, divided by the total tumor area.

[00226] In some embodiments, the cells of the lung cancer have intermediate or high tumor mutational burden, optionally wherein the tumor has more than 5 or between 5 and 20 mutations, more than 20 or between 20 and 50 mutations, or more than 50 mutations.

[00227] In some embodiments, the cells of the lung cancer comprise an epidermal growth factor (EGFR) mutation. In some embodiments, the cells of the lung cancer comprise a v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation. In some embodiments, the cells of the lung cancer comprise an ALK mutation.

[00228] In some embodiments, the cells of the lung cancer are EGFR genomic aberration negative. In some embodiments, the cells of the lung cancer are KRAS genomic aberration negative. In some embodiments, the cells of the lung cancer are ALK genomic aberration negative.

[00229] In some embodiments, the NSCLC is characterized by expression of one or more of INSM1, CD56/NCAM, synaptophysin, or chromogranin A. In some embodiments, the NSCLC is characterized by expression of INSM1. In some embodiments, the NSCLC is characterized by

expression of CD56/NCAM. In some embodiments, the NSCLC is characterized by expression of synaptophysin. In some embodiments, the NSCLC is characterized by expression of chromogranin.

[00230] In some embodiments, the NSCLC is characterized by more than 16.3 ng/ml of neuron-specific enolase (NSE). In some embodiments, the NSCLC is characterized by more than 66 pg/ml progastrin-releasing peptide (ProGRP). In some embodiments, the NSCLC is characterized by more than 2.5 ng/ml carcinoembryonic antigen (CEA). In some embodiments, the NSCLC is characterized by more than 10 ng/ml carcinoembryonic antigen (CEA). In some embodiments, the NSCLC is characterized by more than 16.3 ng/ml of neuron-specific enolase (NSE), more than 66 pg/ml progastrin-releasing peptide (ProGRP), and more than 2.5 ng/ml or more than 10 ng/ml carcinoembryonic antigen (CEA).

(f) Patient Populations Treated As Provided Herein

[00231] In some embodiments, the patient is a mammal. In some embodiments, the mammal is human. In some embodiments, the patient is an adult. In some embodiments, the patient is 18 years of age or over 18 years of age. In some embodiments, the patient is over 40 years of age, over 45 years of age, over 50 years of age, over 55 years of age, over 60 years of age, over 65 years of age, over 70 years of age, over 75 years of age, or over 80 years of age. In some embodiments, the patient is 65 years or older.

[00232] In some embodiments, the patient is male. In some embodiments, the patient is female.

[00233] In some embodiments, the patient is a current smoker. In some embodiments, the patient is a former smoker. In some embodiments the patient has never smoked or was never a smoker.

[00234] In some embodiments, the subject has (*e.g.*, has been diagnosed with) a solid cancer. In some embodiments, the subject has (*e.g.*, has been diagnosed with) a resectable solid cancer. In some embodiments, the subject has (*e.g.*, has been diagnosed with) lung cancer. In some embodiments, the subject has (*e.g.*, has been diagnosed with) esophageal cancer. In some embodiments, the subject has any of the cancers described herein. In some embodiments, the

subject has mid-stage lung cancer. In some embodiments, the subject has (*e.g.*, has been diagnosed with) small cell lung cancer. In some embodiments, the subject has (*e.g.*, has been diagnosed with) non-small cell lung cancer (NSCLC). In some embodiments, the subject has (*e.g.*, has been diagnosed) with stage I NSCLC. In some embodiments, the subject has (*e.g.*, has been diagnosed) with stage IIA NSCLC. In some embodiments, the subject has (*e.g.*, has been diagnosed) with stage IIB or IIIA NSCLC. In some embodiments, the subject has (*e.g.*, has been diagnosed) with squamous cell carcinoma. In some embodiments, the subject has (*e.g.*, has been diagnosed) non-squamous small cell carcinoma.

**[00235]** In some embodiments, the subject has (*e.g.*, has been diagnosed with) esophageal cancer. In some embodiments, the subject has (*e.g.*, has been diagnosed with) esophageal squamous cell carcinoma (*e.g.*, resectable esophageal squamous cell carcinoma). In some embodiments, the subject has (*e.g.*, has been diagnosed) with stage I esophageal squamous cell carcinoma. In some embodiments, the subject has (*e.g.*, has been diagnosed) with stage IIA esophageal squamous cell carcinoma. In some embodiments, the subject has (*e.g.*, has been diagnosed) with stage IIB or IIIA esophageal squamous cell carcinoma. In some embodiments, the subject has (*e.g.*, has been diagnosed) with stage IV esophageal squamous cell carcinoma. In some embodiments, the subject has (*e.g.*, has been diagnosed) with stage cT1-2N+M0 esophageal squamous cell carcinoma. In some embodiments, the subject has (*e.g.*, has been diagnosed) with stage cT3NanyM0 esophageal squamous cell carcinoma. In some embodiments, the subject has (*e.g.*, has been diagnosed) with esophageal adenocarcinoma.

**[00236]** In some embodiments, the subject has (*e.g.*, has been diagnosed with) metastatic cancer. In some embodiments, the subject has one or more of liver, lung, lymph node, bone, and/or adrenal gland metastasis. In some embodiments, the subject has liver, lung or lymph node metastasis. In some embodiments, the subject has liver metastasis. In some embodiments, the subject has lung metastasis. In some embodiments, the subject has lymph node metastasis. In some embodiments, the subject has bone metastasis. In some embodiments, the subject has adrenal gland metastasis. In some embodiments, the subject has 1, 2, 3, or more metastatic sites. In some embodiments, the subject has 1 or more metastatic sites. In some embodiments, the subject has 2 or more metastatic sites. In some embodiments, the subject has 3 or more

metastatic sites. In some embodiments, the subject does not have brain metastasis. In other embodiments, the subject has brain metastasis.

**[00237]** In some embodiments, the subject has been diagnosed using histological markers. In some embodiments, the subject has been diagnosed using cytological markers. In some embodiments, the subject has been diagnosed using histological and cytological markers. In some embodiments, the subject has been diagnosed using a biopsy. In some embodiments, the subject has been diagnosed using a solid biopsy. In some embodiments, the subject has been diagnosed with a liquid biopsy. Solid tissue biopsy involves sampling a piece of tissue from a node or tumor for examination. Liquid biopsy is a minimally invasive approach for sample procurement, mostly body fluids, and it is used to detect molecular alterations in shed, circulating tumor cells.

**[00238]** In some embodiments, the subject has not previously been treated with an immunotherapy. In some embodiments, the subject has not previously been treated with a chemotherapy (*e.g.*, platinum-based chemotherapy). In some embodiments, the subject has not previously been treated with any immune checkpoint inhibitor. In some embodiments, the subject has not previously been treated with an immunotherapy or a chemotherapy. In some embodiments, the subject has not previously been treated with an immunotherapy and/or a chemotherapy for the cancer being treated in accordance with the methods described herein. In some embodiments, the subject has not received prior chemotherapy for NSCLC. In some of the embodiments where the subject has been treated for limited stage NSCLC, there is a treatment-free interval of 6 months or more before the diagnosis of NSCLC and/or the initiation of the treatment described herein. In some embodiments, the subject has not received prior therapy (*e.g.*, chemotherapy) for esophageal squamous cell carcinoma. In some embodiments, the subject has not received systemic treatment with either corticosteroids or other immunosuppressive agents within 14 days of treatment described herein.

**[00239]** In some embodiments, the subject has received prior chemotherapy treatment (*e.g.*, for the cancer being treated). In some embodiments, the subject has received prior immunotherapy treatment (*e.g.*, for the cancer being treated).

**[00240]** In some embodiments, the subject has adequate organ function, *e.g.*, as measured by

one or more of the criteria described herein.

[00241] In some embodiments, the subject has no renal dysfunction. In some embodiments, the subject does not have severe renal dysfunction. In some embodiments, the subject has a moderate renal dysfunction as described herein. In some embodiments, the subject has glomerular filtration rate of more than 30 mL/min/1.73 m<sup>2</sup> and less than 60 mL/min/1.73 m<sup>2</sup> by Chronic Kidney Disease Epidemiology Collaboration equation.

(g) Uses and Methods of Treatment Provided Herein

[00242] In some embodiments, the neoadjuvant and adjuvant treatment of resectable NSCLC comprises platinum-based doublet chemotherapy with either cisplatin or carboplatin for patients with comorbidities or who are not able to tolerate cisplatin (NCCN Guideline 2019, Postmus et al 2017; CSCO 2018). Either platinum may be combined with a variety of chemotherapeutics, including vinorelbine, etoposide, gemcitabine, docetaxel, paclitaxel and pemetrexed. In some embodiments, neoadjuvant chemotherapy may consist of platinum in combination with either pemetrexed or paclitaxel for patients with non-squamous and squamous histology, respectively. Dosing of chemotherapeutics are summarized in the Table below.

[00243] In some embodiments, the disclosure relates to a method of treating lung cancer (such as NSCLC) or esophageal cancer (e.g., esophageal squamous cell carcinoma) in a subject (e.g., a human), the method comprising administering to the subject effective amounts of an anti-PD-1 antibody and one or more chemotherapeutic drug (e.g., a platinum chemotherapy drug). In some embodiments, the one or more chemotherapeutic drugs is cisplatin or carboplatin. In some embodiments, the one or more chemotherapeutic drugs is pemetrexed or paclitaxel. In some embodiments, the one or more chemotherapeutic drugs is etoposide. In some embodiments, the one or more chemotherapeutic drugs is 5-fluorouracil.

[00244] In some embodiments, the disclosure relates to a method of treating lung cancer (such as NSCLC) or esophageal cancer (e.g., esophageal squamous cell carcinoma) in a subject (e.g., a human), the method comprising administering to the subject an effective amounts of an anti-PD-1 antibody, cisplatin or carboplatin, and pemetrexed or paclitaxel or 5-fluorouracil. In some embodiments, the subject is treated in accordance with a treatment regimen (such as dosing,



frequency and duration of the treatment) described herein.

**[00245]** The anti-PD-1 antibody and one or more chemotherapeutic drugs disclosed herein may be administered parenterally. The term “parenteral” as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques. In some embodiments, the anti-PD-1 antibody and chemotherapeutic drug(s) may be administered by different routes. In some embodiments, the anti-PD-1 antibody is administered intravenously, and the one or more chemotherapeutic drugs are also administered intravenously.

**[00246]** In some embodiments, described herein is a method of treating lung cancer (*e.g.*, NSCLC) or esophageal cancer (*e.g.*, esophageal squamous cell carcinoma) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an anti-PD-1 antibody, wherein the PD-1 antibody comprises (i) a heavy chain variable region comprising complementarity determining region (CDR)-H1 comprising SEQ ID NO:31, CDR-H2 comprising SEQ ID NO:32, and CDR-H3 comprising SEQ ID NO:33, and (ii) a light chain variable region comprising CDR-L1 comprising SEQ ID NO:34, CDR-L2 comprising SEQ ID NO:35, and CDR-L3 comprising SEQ ID NO:36, and a therapeutically effective amount of one or more chemotherapeutic drugs. In some embodiments, described herein is a method of treating lung cancer (*e.g.*, NSCLC) or esophageal cancer (*e.g.*, esophageal squamous cell carcinoma) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an anti-PD-1 antibody, wherein the PD-1 antibody comprises a heavy chain variable region (Vh) and a light chain variable region (Vl) comprising SEQ ID NO:24 and SEQ ID NO:26, respectively, and a therapeutically effective amount of one or more chemotherapeutic drugs. In some embodiments, described herein is a method of treating lung cancer (*e.g.*, NSCLC) or esophageal cancer (*e.g.*, esophageal squamous cell carcinoma) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an anti-PD-1 antibody, wherein the PD-1 antibody is a monoclonal antibody or a fragment thereof (*e.g.*, a humanized antibody or fragment), comprising a heavy chain variable region (Vh) amino acid sequence of SEQ ID NO:24, a light chain variable region (Vl) amino acid sequence of SEQ ID NO:26, and an IgG4 constant domain amino acid sequence of SEQ ID NO:88. In some

embodiments, described herein is a method of treating lung cancer (*e.g.*, NSCLC) or esophageal cancer (*e.g.*, esophageal squamous cell carcinoma) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Tislelizumab and a therapeutically effective amount of one or more chemotherapeutic drugs. In some embodiments, a subject is administered one or more, or all of the study drugs provided in **Table 6**, at the treatment regimen described therein. In some embodiments, the choice between cisplatin and carboplatin is at treating physician's discretion.

| <b>Table 6: Selection and Timing of Dose for Each Patient</b> |                       |                                    |                                |                                                               |
|---------------------------------------------------------------|-----------------------|------------------------------------|--------------------------------|---------------------------------------------------------------|
| <b>Study Drug</b>                                             | <b>Dose</b>           | <b>Frequency of Administration</b> | <b>Route of Administration</b> | <b>Duration of Treatment</b>                                  |
| Tislelizumab                                                  | 200 mg                | Day 1 of every 3 weeks             | IV                             | 3 to 4 cycles during the neoadjuvant phase                    |
| Placebo                                                       | NA                    | Day 1 of every 3 weeks             | IV                             |                                                               |
| Tislelizumab                                                  | 400 mg                | Day 1 of every 6 weeks             | IV                             | Up to 8 cycles during the adjuvant phase                      |
| Placebo                                                       | NA                    | Day 1 of every 6 weeks             | IV                             |                                                               |
| Cisplatin                                                     | 75 mg/m <sup>2</sup>  | Day 1 of every 3 weeks             | IV                             | 3 to 4 cycles during the neoadjuvant phase                    |
| Carboplatin                                                   | AUC of 5 mg/mL/min    | Day 1 of every 3 weeks             | IV                             |                                                               |
| Pemetrexed                                                    | 500 mg/m <sup>2</sup> | Day 1 of every 3 weeks             | IV                             | 3 to 4 cycles during the neoadjuvant phase (for non-squamous) |
| Paclitaxel                                                    | 175 mg/m <sup>2</sup> | Days 1 of every 3 weeks            | IV                             | 3 to 4 cycles during the neoadjuvant phase (for squamous)     |

Abbreviation: AUC, area under the curve; IV, intravenous(ly); NA, not applicable.

(h) Anti-PD-1 Antibody Dose of 200 mg Once Every 3 Weeks in Neoadjuvant Phase

[00247] Provided herein is an anti-PD-1 antibody (Tislelizumab) at the dose of 200 mg once every 3 weeks. In particular, a fixed dose of 200 mg Tislelizumab for intravenous administration once every 3 weeks during neoadjuvant phase is described herein.

(i) Anti-PD-1 Antibody Dose of 400 mg Once Every 6 Weeks in Adjuvant Phase

[00248] Further provided herein is an anti-PD-1 antibody (Tislelizumab) at the dose of 400 mg once every 6 weeks. This dosage was selected for the adjuvant phase by matching dose and exposure (AUC) with the exposure of 200 mg once every 3 weeks regimen during the neoadjuvant phase. In some embodiments, provided herein is an administration regimen comprising administering Tislelizumab 200 mg once every 3 weeks during neoadjuvant phase, followed by 400 mg once every 6 weeks during adjuvant phase.

(j) Chemotherapy

[00249] In some embodiments, patients may receive treatment with platinum-based doublet chemotherapy during the neoadjuvant phase (**Table 6**). In some embodiments, patients may receive treatment with 5-fluorouracil and cisplatin during the neoadjuvant phase.

[00250] In some embodiments, Cisplatin 75 mg/m<sup>2</sup> may be administered as an intravenous infusion over 2 hours on Day 1 of each 3 week cycle for 3 to 4 cycles.

[00251] In some embodiments, Carboplatin AUC of 5 mg/mL/min may be administered as an intravenous infusion over 1 hour on Day 1 of each 3-week cycle for 3 to 4 cycles. Carboplatin can replace cisplatin per the investigator's discretion in consideration of patient's tolerability to cisplatin.

[00252] In some embodiments, for non-squamous: Pemetrexed 500 mg/m<sup>2</sup> may be administered as an intravenous infusion over 10 minutes on Day 1 of each 3-week cycle for 3 to 4 cycles.

[00253] In some embodiments, for squamous: Paclitaxel 175 mg/m<sup>2</sup> may be administered as an intravenous infusion over 3 hours on Day 1 of each 3-week cycle for 3 to 4 cycles.

[00254] In some embodiments, the length of infusion period for cisplatin, carboplatin,

pemetrexed, paclitaxel, and 5-fluorouracil could also follow the approved label or local practice. The administered dose may be adjusted within  $\pm 5\%$  of the calculated dose at the investigator's discretion.

**[00255]** Embodiments of the present disclosure also include the agents and combinations described herein (i) for use in, (ii) for use as a medicament or composition for, or (iii) for use in the preparation of a medicament for:

- b. therapy (*e.g.*, of the human body);
- c. medicine;
- d. induction of or augmenting an anti-tumor immune response;
- e. decreasing the number of one or more tumor markers in a patient;
- f. halting or delaying the growth of the cancer described herein;
- g. halting or delaying the progression of the cancer described herein;
- h. halting or delaying the progression of the cancer described herein;
- i. stabilization of the cancer;
- j. inhibiting the growth or survival of the cancer cells;
- k. eliminating or reducing the size of one or more cancerous lesions;
- l. reduction of the progression, onset or severity of the cancer described herein;
- m. reducing the severity or duration of the clinical symptoms of the cancer described herein;
- n. prolonging the survival of a patient relative to the expected survival in a similar untreated patient;
- o. inducing a major pathological response (MPR), or complete or partial remission of the cancer described herein; or
- p. treatment of the cancer described herein.

*A. Response to Treatment*

**[00256]** In some embodiments, the treating is clinically effective or the subject is a responder to the treating by at least one measure of response to treatment. In some embodiments, the response to treatment is measured by overall survival, progression-free or event-free survival, major pathological response ("MPR"), pathological complete response ("pCR"), overall

response, partial response, duration of response, and/or tumor volume, diameter or size. In some embodiments, the response to treatment is measured by tumor volume. In some embodiments, the treating reduces tumor volume by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, or at least 75%. In some embodiments, the subject has greater than 30% probability of survival at 24 months. In some embodiments, the treating is effective as demonstrated by patient population overall survival rate at 24 months of greater than 30%. In some embodiments, the subject has greater than 15% or 20% probability of event-free survival at 12 months. In some embodiments, the treating is effective as demonstrated by a patient population event-free survival rate at 12 months of greater than 20%.

**[00257]** In some embodiments, the response to treatment is measured by a major pathological response (“MPR”), which is defined as less than 10% residual viable tumor after neoadjuvant therapy. In some embodiments, the MPR is twice that observed in the control group. In some embodiments, the MPR is at least 25%. In some embodiments, the treating results in the MPR in the subject. In some embodiments, the MPR is at least twice that observed in the control group not treated with the anti-PD-1 antibody. In some embodiments, the subject has at least 25%, 35%, 40%, 45% or 50% probability of the MPR. In some aspects, the treating is effective as demonstrated by patient population MPR of at least 25%, 35%, 40%, 45% or 50%. In some embodiments, the treating results in the pCR in the subject. In some embodiments, the subject has at least 15%, 20%, 25%, 30%, 35%, or 40% probability of the pCR. In some embodiments, the treating is effective as demonstrated by patient population pCR of at least 15%, 20%, 25%, 30%, 35%, or 40%.

**[00258]** Adopting meaningful surrogate endpoints may expedite the evaluation of new therapeutics in cancer treatment. Pathological response as a surrogate endpoint is adopted in breast cancer. Studies for breast cancer have used pathological complete response (pCR) for evaluating the efficacy of neoadjuvant treatment. However, the incidence of pCR rates has varied in neoadjuvant NSCLC studies. Thus, major pathological response (MPR) after surgical resection of NSCLC has been proposed as a surrogate endpoint based on 3 findings: 1) pathological response strongly correlates to OS; 2) pathological response is reflective of

neoadjuvant chemotherapy; and 3) the degree of pathological response correlates with the degree of OS benefit (Hellmann et al 2014).

**[00259]** In some embodiments, the patient is responsive to treatment by one, two, three or more criteria described herein and/or known in the art. In some embodiments, the responsiveness criteria are any criterial described herein, including but not limited to those described in the example section of this application.

**[00260]** In some embodiments, the treatment described herein reduces tumor volume, size, or diameter. In some embodiments, the treatment described herein reduces tumor volume, size or diameter by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%. In some embodiments, the treatment described herein reduces the diameter of a cancer lesion by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%. In some embodiments, the measurements are made by CT or MRI. In some embodiments, the measurements are made and results are assessed as described herein (see, *e.g.*, the example section). In some embodiments, the reduction is relative to the tumor volume, size or diameter in the subject prior to the start of the treatment.

**[00261]** In some embodiments, the methods described herein improve overall survival. In some embodiments, the improvement is relative to probability of survival without treatment or with a standard of care treatment.

**[00262]** In some embodiments, the response to treatment in a subject is measured by overall survival, progression-free survival, event-free survival, overall response rate, objective response rate, partial response, duration of response, or a combination thereof. In some embodiments, the response to treatment in a subject is measured by overall survival. In some embodiments, the response to treatment in a subject is measured by progression-free survival. In some embodiments, the response to treatment in a subject is measured by event-free survival. In some embodiments, the response to treatment in a subject is measured by overall response rate. In

some embodiments, the response to treatment in a subject is measured by objective response rate. In some embodiments, the response to treatment in a subject is measured by partial response. In some embodiments, the response to treatment in a subject is measured by duration of response.

**[00263]** In some embodiments, the patient survives for at least 24 months. In some embodiments, the patient survives for at least 27 months. In some embodiments, the patient survives for at least 30 months. In some embodiments, the patient survives for at least 36 months. In some embodiments, the patient survives for at least 39 months. In some embodiments, the patient survives for at least 42 months. In some embodiments, the patient survives for at least 45 months. In some embodiments, the patient survives for at least 48 months or at least 4 years. In some embodiments, the patient survives for at least 5 years. In some embodiments, the survival determination is starting from the initiation of treatment (*e.g.*, the specified months since the treatment initiation).

**[00264]** In some embodiments, the subject has a greater than 30% probability of survival at 24 months from initiation of a treatment regimen described herein. In some embodiments, the treating prolongs survival of the human patient which prolonged survival can be free of progression of the lung cancer. In some embodiments, the treating prolongs survival of the human patient which prolonged survival can be free of progression of the small cell lung cancer. In some embodiments, the subject has a greater than 15% probability of event-free survival at 12 months from initiation of a treatment regimen described herein. In some embodiments, the subject has a greater than 20% probability of event-free survival at 12 months from initiation of a treatment regimen described herein.

**[00265]** In some embodiments, the patient survives free of progression of the NSCLC for at least 4 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 5 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 6 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 7 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 8 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 9 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 10 months. In some embodiments, the patient survives

free of progression of the NSCLC for at least 11 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 12 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 15 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 18 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 21 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 24 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 30 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 34 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 35 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 36 months or 3 years. In some embodiments, the patient survives free of progression of the NSCLC for at least 39 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 42 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 45 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 48 months or 4 years. In some embodiments, the patient survives free of progression of the NSCLC for at least 5 years. In some embodiments, the survival free of progression determination is starting from the initiation of treatment (*e.g.*, the specified months since the treatment initiation).

**[00266]** In some embodiments, the patient survives free of progression of the esophageal squamous cell carcinoma (ESCC) (*e.g.*, resectable ESCC) for at least 4 months. In some embodiments, the patient survives free of progression of the ESCC (*e.g.*, resectable ESCC) for at least 5 months. In some embodiments, the patient survives free of progression of the ESCC (*e.g.*, resectable ESCC) for at least 6 months. In some embodiments, the patient survives free of progression of the ESCC (*e.g.*, resectable ESCC) for at least 7 months. In some embodiments, the patient survives free of progression of the ESCC (*e.g.*, resectable ESCC) for at least 8 months. In some embodiments, the patient survives free of progression of the ESCC (*e.g.*, resectable ESCC) for at least 9 months. In some embodiments, the patient survives free of progression of the ESCC (*e.g.*, resectable ESCC) for at least 10 months. In some embodiments, the patient survives free of progression of the ESCC (*e.g.*, resectable ESCC) for at least 11 months. In some embodiments, the patient survives free of progression of the ESCC (*e.g.*,



resectable ESCC) for at least 12 months. In some embodiments, the patient survives free of progression of the ESCC (e.g., resectable ESCC) for at least 15 months. In some embodiments, the patient survives free of progression of the ESCC (e.g., resectable ESCC) for at least 18 months. In some embodiments, the patient survives free of progression of the ESCC (e.g., resectable ESCC) for at least 21 months. In some embodiments, the patient survives free of progression of the NSCLC for at least 24 months. In some embodiments, the patient survives free of progression of the ESCC (e.g., resectable ESCC) for at least 30 months. In some embodiments, the patient survives free of progression of the ESCC (e.g., resectable ESCC) for at least 34 months. In some embodiments, the patient survives free of progression of the ESCC (e.g., resectable ESCC) for at least 35 months. In some embodiments, the patient survives free of progression of the ESCC (e.g., resectable ESCC) for at least 36 months or 3 years. In some embodiments, the patient survives free of progression of the ESCC (e.g., resectable ESCC) for at least 39 months. In some embodiments, the patient survives free of progression of the ESCC (e.g., resectable ESCC) for at least 42 months. In some embodiments, the patient survives free of progression of the ESCC (e.g., resectable ESCC) for at least 45 months. In some embodiments, the patient survives free of progression of the ESCC (e.g., resectable ESCC) for at least 48 months or 4 years. In some embodiments, the patient survives free of progression of the ESCC (e.g., resectable ESCC) for at least 5 years. In some embodiments, the survival free of progression determination is starting from the initiation of treatment (*e.g.*, the specified months since the treatment initiation).

**[00267]** In some embodiments, the patient exhibits the duration of response of at least 6 months. In some embodiments, the patient exhibits the duration of response of at least 12 months. In some embodiments, the patient exhibits the duration of response of at least 18 months. In some embodiments, the patient exhibits the duration of response of at least 24 months. In some embodiments, the patient exhibits the duration of response of at least 30 months. In some embodiments, the patient exhibits the duration of response of at least 33 months. In some embodiments, the patient exhibits the duration of response of at least 36 months. In some embodiments, the patient exhibits the duration of response of at least 39 months. In some embodiments, the patient exhibits the duration of response of at least 42 months. In some embodiments, the patient exhibits the duration of response of at least 45

months. In some embodiments, the patient exhibits the duration of response of at least 48 months or 4 years. In some embodiments, the patient exhibits the duration of response of at least 5 years. In some embodiments, the responsiveness determination is starting from the initiation of treatment (*e.g.*, the specified months since the treatment initiation).

[00268] In some embodiments, the response to treatment in a subject is measured by overall response rate, complete response and/or partial response. In some embodiments, the determination of these responsiveness endpoints are determined using RECIST v1.1.

[00269] In some embodiments, a human responder to treatment exhibits stable disease. In some embodiments, a human responder to treatment exhibits stable disease for, or at least for, 3 months, 6 months, 9 months, 12 months, 18 months, 21 months, 24 months, 30 months, 36 months, 42 months, 48 months or 5 years. In some embodiments, the determination is starting from the initiation of treatment (*e.g.*, the specified months since the treatment initiation).

[00270] In some embodiments, a human responder to treatment does not exhibit progressive disease, and/or exhibits delay in the cancer progression. In some embodiments, a human responder to treatment does not exhibit progressive disease, and/or exhibits delay in the cancer progression for, or at least for, 3 months, 6 months, 9 months, 12 months, 18 months, 21 months, 24 months, 30 months, 36 months, 42 months, 48 months or 5 years. In some embodiments, the determination is starting from the initiation of treatment (*e.g.*, the specified months since the treatment initiation).

[00271] In some embodiments, a human responder to treatment exhibits a response (such as an improvement or delay of progression response) in one or more patient-reported outcome (PRO) assessments, such as any one of the PRO assessments described herein (including but not limited to Quality of Life assessments using any of the Questionnaires described herein). In some embodiments, a positive response on a PRO assessment is observed for, or at least for, 3 months, 6 months, 9 months, 12 months, 18 months, 21 months, 24 months, 30 months, 36 months, 42 months, 48 months or 5 years starting from the initiation of treatment.

[00272] In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for a resectable NSCLC. In some embodiments, a human responder to

treatment as described herein has been diagnosed and treated for Stage I NSCLC. In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for Stage IIA NSCLC. In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for Stage IIB NSCLC. In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for Stage IIIA NSCLC. In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for Stage IIIB NSCLC. In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for Stage IV NSCLC. In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for NSCLC. In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for metastatic NSCLC.

**[00273]** In some embodiments, a human responder to treatment is free of progression of a resectable NSCLC. In some embodiments, a human responder to treatment is free of progression of Stage I NSCLC. In some embodiments, a human responder to treatment is free of progression of Stage IIA NSCLC. In some embodiments, a human responder to is free of progression of Stage IIB NSCLC. In some embodiments, a human responder to treatment is free of progression of Stage IIIA NSCLC. In some embodiments, a human responder to treatment is free of progression of Stage IIIB NSCLC. In some embodiments, a human responder to treatment is free of progression of Stage IV NSCLC. In some embodiments, a human responder to treatment is free of progression of NSCLC. In some embodiments, a human responder to treatment is free of progression of metastatic NSCLC.

**[00274]** In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for a resectable ESCC. In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for Stage I ESCC. In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for Stage IIA ESCC. In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for Stage IIB ESCC. In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for Stage IIIA ESCC. In some embodiments, a human responder to treatment as described herein has been diagnosed

and treated for Stage IIIB ESCC. In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for Stage IV ESCC. In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for ESCC (e.g., resectable ESCC). In some embodiments, a human responder to treatment as described herein has been diagnosed and treated for metastatic ESCC.

[00275] In some embodiments, a human responder to treatment is free of progression of a resectable ESCC. In some embodiments, a human responder to treatment is free of progression of Stage I ESCC. In some embodiments, a human responder to treatment is free of progression of Stage IIA ESCC. In some embodiments, a human responder to is free of progression of Stage IIB ESCC. In some embodiments, a human responder to treatment is free of progression of Stage IIIA ESCC. In some embodiments, a human responder to treatment is free of progression of Stage IIIB ESCC. In some embodiments, a human responder to treatment is free of progression of Stage IV ESCC. In some embodiments, a human responder to treatment is free of progression of ESCC. In some embodiments, a human responder to treatment is free of progression of metastatic ESCC.

(a) Pharmaceutical Compositions

[00276] Provided herein are compositions, including pharmaceutical formulations, comprising an anti-PD-1 antibody or an antigen-binding fragment thereof described herein. Also provided herein are compositions, including pharmaceutical formulations, comprising one or more chemotherapeutic drugs described herein. In some embodiments, the composition, including a pharmaceutical formulation, comprises an anti-PD-1 antibody or an antigen-binding fragment thereof and one or more chemotherapeutic drugs.

[00277] Pharmaceutical formulations of an anti-PD-1 antibody or antigen-binding fragment as described herein are prepared by mixing such antibody or antigen-binding fragment having the desired degree of purity with one or more optional pharmaceutically acceptable carriers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not

limited to buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3- pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as polyethylene glycol (PEG). In some embodiments, the surfactant is a polysorbate. Exemplary pharmaceutically acceptable carriers herein further include interstitial drug dispersion agents such as soluble neutral-active hyaluronidase glycoproteins (sHASEGP), for example, human soluble PH-20 hyaluronidase glycoproteins, such as rHuPH20 (HYLENEX®, Baxter International, Inc.). Certain exemplary sHASEGPs and methods of use, including rHuPH20, are described in US Patent Nos. US 7,871,607 and 2006/0104968. In one aspect, a sHASEGP is combined with one or more additional glycosaminoglycanases such as chondroitinases.

[00278] Exemplary lyophilized antibody formulations are described in US Patent No. 6,267,958. Aqueous antibody formulations include those described in US Patent No. 6,171,586 and WO2006/044908, the latter formulations including a histidine-acetate buffer. In some embodiments, the formulations include a histidine-citric acid buffer. Sustained-release preparations can be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. The formulations to be used for *in vivo* administration are generally sterile. Sterility can be readily accomplished, *e.g.*, by filtration through sterile filtration membranes.

[00279] [000333] In some embodiments, the pharmaceutical composition or formulation comprises a formulation buffer comprising histidine, acetate, citrate, succinate, phosphate,

mixture of histidine and acetic acid, mixture of histidine and citric acid, salt or hydrate thereof, or any combination of them. In some embodiments, the formulation buffer comprises a histidine buffer that comprises histidine, histidine hydrochloride, L-histidine, L-histidine hydrochloride, L-histidine hydrochloride hydrate, L-histidine hydrochloride monohydrate, or a combination thereof. In some embodiments, the histidine buffer comprises L-histidine/L-histidine hydrochloride monohydrate buffer (His/His HCl). In some embodiments, the histidine buffer comprises histidine/L-histidine hydrochloride monohydrate buffer and citric acid monohydrate. In some embodiments, the concentration of the histidine buffer (e.g., L-histidine/L-histidine hydrochloride monohydrate) is between about 5 mM to about 30 mM. In some embodiments, the concentration of the histidine buffer (e.g., L-histidine/L-histidine hydrochloride monohydrate) is between about 5 mM to about 10 mM, between about 5 mM to about 15 mM, between about 5 mM to about 20 mM, between about 10 mM to about 15 mM, between about 10 mM to about 20 mM, between about 10 mM to about 25 mM, between about 15 mM to about 20 mM, between about 15 mM to about 25 mM, between about 15 mM to about 30 mM, between about 20 mM to about 25 mM, or between about 25 mM to about 30 mM. In some embodiments, the concentration of the histidine buffer (e.g., L-histidine/L-histidine hydrochloride monohydrate) is about 5 mM or more, about 10 mM or more, about 15 mM or more, about 20 mM or more, about 25 mM or more, about 30 mM or more. In some embodiments, the concentration of the histidine buffer (e.g., L-histidine/L-histidine hydrochloride monohydrate) is 10mM.

**[00280]** In some embodiments, the concentration of the histidine is about 5-15 mM, in a preferred embodiment the concentration of histidine is about 11 mM. In some embodiments, the concentration of the L-histidine hydrochloride monohydrate is about 1-5 mM, in a preferred embodiment the concentration of L-histidine hydrochloride monohydrate is about 4 mM. In some embodiments, the formulation comprises histidine at a concentration of about 5-15 mM, in a preferred embodiment the concentration of histidine is about 11 mM, and L-histidine hydrochloride monohydrate at a concentration of about 1-5 mM, in a preferred embodiment the concentration of L-histidine hydrochloride monohydrate is about 4 mM. In some embodiments, the formulation buffer is a mixture of histidine, L-histidine hydrochloride monohydrate, citric acid monohydrate, and sodium citrate; wherein the formulation comprises histidine at a

concentration of about 5-15 mM, in a preferred embodiment the concentration of histidine is about 11 mM, and L-histidine hydrochloride monohydrate at a concentration of about 1-5 mM, in a preferred embodiment the concentration of L-histidine hydrochloride monohydrate is about 4 mM, wherein the citric acid monohydrate is at a concentration of about 1-5 mM, preferably 2 mM, and sodium citrate is present at a concentration of 15- 30 mM, preferably about 23 mM.

[00281] [000335] In some embodiments, the pharmaceutical composition or formulation comprises a stabilizer. In some embodiments, the stabilizer comprises trehalose, sucrose, sorbitol, mannitol, L-arginine hydrochloride, maltose, dextran, (2-hydroxypropyl)- $\beta$ -cyclodextrin, sodium chloride, magnesium chloride, calcium chloride, sodium sulfate, sodium dihydrogen phosphate, disodium hydrogen phosphate, or a combination thereof. In some embodiments, the stabilizer comprises trehalose, sucrose, L-arginine hydrochloride, sodium chloride, or a combination thereof. In some embodiments, the stabilizer is trehalose. In some embodiments the trehalose is  $\alpha$ -trehalose dihydrate. In some embodiments, the concentration of the stabilizer is between about 50 mM to about 300 mM. In some embodiments, the concentration of the stabilizer is between about 50 mM to about 100 mM, between about 50 mM to about 150 mM, between about 50 mM to about 200 mM, between about 100 mM to about 150 mM, between about 100 mM to about 200 mM, between about 100 mM to about 250 mM, between about 150 mM to about 200 mM, between about 150 mM to about 250 mM, or between about 150 mM to about 300 mM. In some embodiments, the concentration of the stabilizer is about 50 mM or more, about 60 mM or more, about 70 mM or more, about 80 mM or more, about 90 mM or more, about 100 mM or more, about 110 mM or more, about 120 mM or more, about 130 mM or more, about 140 mM or more, about 150 mM or more, about 160 mM or more, about 170 mM or more, about 180 mM or more, about 190 mM or more, about 200 mM or more, about 210 mM or more, about 220 mM or more, about 230 mM or more, about 240 mM or more, about 250 mM or more, about 260 mM or more, about 270 mM or more, about 280 mM or more, about 290 mM or more, or about 300 mM or more. In some embodiments, the concentration of the stabilizer is about 190 mM.

[00282] In some embodiments, the pharmaceutical composition or formulation comprises a non-ionic surfactant. In some embodiments, the non-ionic surfactant comprises polysorbate 80

(PS80), polysorbate 20 (PS20), poloxamer188 (P188), or a combination thereof. In some embodiments, the non-ionic surfactant is PS20. In some embodiment, the concentration of the non-ionic surfactant is between about 0.01% to about 1%. In some embodiments, the concentration of the non-ionic surfactant is between about 0.01% to about 0.03%, between about 0.01% to about 0.06%, between about 0.01% to about 0.09%, between about 0.03% to about 0.06%, between about 0.03% to about 0.09%, between about 0.03% to about 0.2%, between about 0.06% to about 0.09%, between about 0.06% to about 0.2%, between about 0.06% to about 0.5%, between about 0.09% to about 0.2%, between about 0.09% to about 0.5%, between about 0.09% to about 0.8%, between about 0.2% to about 0.5%, between about 0.2% to about 0.8%, between about 0.2% to about 1%, between about 0.5% to about 0.8%, between about 0.5% to about 1%, or between about 0.8% to about 1%. In some embodiments, the concentration of the non-ionic surfactant is about 0.01% or more, is about 0.02% or more, is about 0.03% or more, is about 0.04% or more, is about 0.05% or more, is about 0.06% or more, is about 0.07% or more, is about 0.08% or more, is about 0.09% or more, is about 0.1% or more, is about 0.2% or more, is about 0.3% or more, is about 0.4% or more, is about 0.5% or more, is about 0.6% or more, is about 0.7% or more, is about 0.8% or more, is about 0.9% or more, or is about 1% or more. In some embodiments, the concentration of the non-ionic surfactant is 0.2%.

**[00283]** In some embodiments, the pharmaceutical composition or formulation comprises between about 1 mg/ml to about 10 mg/ml of the antibody such as tislelizumab as disclosed herein. In some embodiments, the pharmaceutical composition or formulation comprises between about 1 mg/ml to about 2 mg/ml, between about 1 mg/ml to about 3 mg/ml, between about 1 mg/ml to about 4 mg/ml, between about 2 mg/ml to about 3 mg/ml, between about 2 mg/ml to about 4 mg/ml, between about 2 mg/ml to about 5 mg/ml, between about 3 mg/ml to about 4 mg/ml, between about 3 mg/ml to about 5 mg/ml, between about 3 mg/ml to about 6 mg/ml, between about 4 mg/ml to about 5 mg/ml, between about 4 mg/ml to about 6 mg/ml, between about 4 mg/ml to about 7 mg/ml, between about 5 mg/ml to about 6 mg/ml, between about 5 mg/ml to about 7 mg/ml, between about 5 mg/ml to about 8 mg/ml, between about 6 mg/ml to about 7 mg/ml, between about 6 mg/ml to about 8 mg/ml, between about 6 mg/ml to about 9 mg/ml, between about 7 mg/ml to about 8 mg/ml, between about 7 mg/ml to about 9 mg/ml, between about 7 mg/ml to about 10 mg/ml, between about 8 mg/ml to about 9 mg/ml,



between about 8 mg/ml to about 10 mg/ml, or between about 9 mg/ml to about 10 mg/ml of the antibody disclosed herein. In some embodiments, the pharmaceutical composition or formulation comprises about 1 mg/ml or more, 2 mg/ml or more, 3 mg/ml or more, 4 mg/ml or more, 5 mg/ml or more, 6 mg/ml or more, 7 mg/ml or more, 8 mg/ml or more, 9 mg/ml or more, or 10 mg/ml or more of the antibody disclosed herein. In some embodiments, the pharmaceutical composition or formulation comprises 10 mg/ml of the antibody (*e.g.* PD-1 antibody or tislelizumab) disclosed herein.

[00284] In some embodiments, the pharmaceutical composition or formulation has a pH of between about 4.5 to about 7.5. In some embodiments, the pharmaceutical composition or formulation has a pH of between about 4.5 to about 5.0, between about 4.5 to about 5.5, between about 4.5 to about 6.0, between about 5.0 to about 5.5, between about 5.0 to about 6.0, between about 5.0 to about 6.5, between about 5.5 to about 6.0, between about 5.5 to about 6.5, between about 5.5 to about 7.0, between about 6.0 to about 6.5, between about 6.0 to about 7.0, between about 6.0 to about 7.5, between about 6.5 to about 7.0, between about 6.5 to about 7.5, or between about 7.0 to about 7.5. In some embodiments, the pharmaceutical composition or formulation has a pH of about 4.5 or more, about 5.0 or more, about 5.5 or more, about 6.0 or more, about 6.5 or more, about 7.0 or more, or about 7.5 or more. In some embodiments, the pharmaceutical composition or formulation has a pH of 6.5.

[00285] In some embodiments, the antibody (*e.g.* PD-1 antibody or tislelizumab) is formulated in a pharmaceutical composition comprising a histidine buffer, a surfactant and a stabilizer. In some embodiments, the surfactant is a polysorbate. In some embodiments, the stabilizer is trehalose. In a particular embodiment, the PD-1 antibody (*e.g.* tislelizumab) is formulated in a pharmaceutical composition comprising citric acid monohydrate, histidine, L-histidine hydrochloride monohydrate, polysorbate 20, sodium citrate, and trehalose.

[00286] The term “pharmaceutical composition” refers to preparations with pharmaceutically acceptable excipients which are in such form as to permit the active ingredients to be effective, and which contains no additional components which are toxic to the subjects to which the composition would be administered. In some embodiments, a pharmaceutical composition may be formulated for administration in solid or liquid form, comprising, without limitation, a form

adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, *e.g.*, those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces. In some aspects, the present disclosure provides compositions, *e.g.*, pharmaceutically acceptable compositions, which include an anti-PD-1 antibody described herein, formulated together with at least one pharmaceutically acceptable excipient.

**[00287]** The term “pharmaceutically acceptable” refers to a molecule or composition that, when administered to a recipient, is not deleterious to the recipient thereof, or that any deleterious effect is outweighed by a benefit to the recipient thereof.

**[00288]** Some examples of materials which may serve as pharmaceutically acceptable carriers comprise: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer’s solution; ethyl alcohol; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in pharmaceutical formulations.

**[00289]** A “pharmaceutically acceptable excipient” includes any and all solvents, dispersion media, isotonic and absorption delaying agents, and the like that are physiologically compatible. The excipient can be suitable for intravenous, intramuscular, subcutaneous, parenteral, rectal, spinal or epidermal administration (*e.g.*, by injection or infusion).

[00290] The compositions disclosed herein can be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.*, injectable and infusion solutions), dispersions or suspensions, liposomes, and suppositories. A suitable form depends on the intended mode of administration and therapeutic application. Typical suitable compositions are in the form of injectable or infusion solutions. One suitable mode of administration is parenteral (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular). In some embodiments, the antibody is administered by intravenous infusion or injection. In some embodiments, the antibody is administered by intramuscular or subcutaneous injection. In some embodiments, the antibody is administered by way of a syringe infusion system.

(b) Kits

[00291] The present disclosure, among other things, provides kits comprising anti-PD-1 antibodies or antigen-binding fragments thereof, and instructions for use and/or administration. In some embodiments, a kit comprises at least one anti-PD-1 antibody or antigen-binding fragment thereof and a pharmaceutically acceptable carrier, and instructions for use and/or administration. In some embodiments, a kit comprises at least one anti-PD-1 antibody or antigen-binding fragment thereof, at least one chemotherapeutic agent, and a pharmaceutically acceptable carrier, and instructions for use and/or administration. In some embodiments, a kit comprises, tislelizumab and one or more chemotherapeutic agents, *e.g.*, cisplatin, carboplatin, pemetrexed, paclitaxel, and/or 5-fluorouracil or any combination thereof, in any dosage described herein or known in the art.

[00292] Also provided are kits for use in various methods disclosed herein. Instructions can comprise a description of administering of one or more pharmaceutical compositions described herein to a subject to achieve an intended activity in a subject. A kit may further comprise a description of selecting a human suitable for treatment based on identifying whether the human is in need of treatment. In some embodiments, instructions comprise a description of administering at least one anti-PD-1 antibody or antigen-binding fragment thereof to a subject who is in need of the treatment.

[00293] Instructions relating to administering one or more doses of at least one anti-PD-1

antibody or antigen-binding fragment thereof, and/or one or more chemotherapeutic drug, generally include information as to dosage, dosing schedule, and route of administration for an intended treatment. Containers may be unit doses, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. Instructions supplied in kits of the disclosure are typically written instructions on a label or package insert. A label or package insert may indicate that one or more pharmaceutical compositions described herein are used for treating, delaying the onset, and/or alleviating a disease, disorder or condition in a subject.

[00294] In some embodiments, kits provided herein are in suitable packaging. Suitable packaging includes, but is not limited to, vials, bottles, jars, flexible packaging, and the like. Also contemplated are packages for use in combination with a specific device, such as an infusion device. A kit may have a sterile access port (for example, a container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). A container may also have a sterile access port.

[00295] Kits can include additional components such as buffers and interpretive information. A kit can comprise a container and a label or one or more package inserts on or associated with a container. In some embodiment, the disclosure provides articles of manufacture comprising contents of kits described above.

[00296] Embodiments described herein are further illustrated by, though in no way limited to, the following examples.

#### (c) Definitions

[00297] For the present disclosure to be more readily understood, certain terms are first defined below. Additional definitions for the following terms and other terms are set forth throughout the Specification.

[00298] While various embodiments and aspects of the present disclosure are shown and described herein, it will be obvious to those skilled in the art that such embodiments and aspects are provided by way of example only. Numerous variations, changes, and substitutions will occur to those skilled in the art without departing from what is disclosed herein. It should be understood that various alternatives to the embodiments disclosed or described herein can be

employed in practicing the instant disclosure.

**[00299]** The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, without limitation, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

**[00300]** 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 this disclosure is related. For example, Juo, *The Concise Dictionary of Biomedicine and Molecular Biology*, 2nd ed., (2001), CRC Press; *The Dictionary of Cell & Molecular Biology*, 5th ed., (2013), Academic Press; and “*The Oxford Dictionary of Biochemistry and Molecular Biology*,” Cammack et al. eds., 2nd ed, (2006), Oxford University Press, provide those of skill in the art with a general dictionary for many of the terms used in this disclosure. Additional definitions of common terms in molecular biology may be found in Benjamin Lewin, *Genes V*, published by Oxford University Press, 1994 (ISBN 0-19 854287-9); Kendrew et al. (eds.), *The Encyclopedia of Molecular Biology*, published by Blackwell Science Ltd., 1994 (ISBN 0-632-02182-9); and Robert A. Meyers (ed.), *Molecular Biology and Biotechnology: A Comprehensive Desk Reference*, published by VCH Publishers, Inc., 1995 (ISBN 1-56081-569-8).

**[00301]** As used herein, including the appended claims, the singular forms of words such as “a,” “an,” and “the,” include their corresponding plural references unless the context clearly dictates otherwise. The term “or” is used to mean, and is used interchangeably with, the term “and/or” unless the context clearly dictates otherwise. The term “and/or” where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term “and/or” as used in a phrase such as “A and/or B” herein is intended to include A and B; A or B; A (alone); and B (alone). Likewise, the term “and/or” as used in a phrase such as “A, B, and/or C” is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

**[00302]** The terms “*e.g.*,” and “*i.e.*,” as used herein, are used merely by way of example,

without limitation intended, and should not be construed as referring only those items explicitly enumerated in the specification.

**[00303]** Unless specifically stated or evident from context, as used herein, the term “about” refers to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, *i.e.*, the limitations of the measurement system. For example, “about” or “comprising essentially of” can mean within one or more than one standard deviation per the practice in the art. “About” or “comprising essentially of” can mean a range of up to 10% (*i.e.*,  $\pm 10\%$ ). Thus, “about” can be understood to be within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, 0.01%, or 0.001% greater or less than the stated value. For example, about 5 mg can include any amount between 4.5 mg and 5.5 mg. Furthermore, particularly with respect to biological systems or processes, the terms can mean up to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the instant disclosure, unless otherwise stated, the meaning of “about” or “comprising essentially of” should be assumed to be within an acceptable error range for that particular value or composition.

**[00304]** The term “about” will be understood by persons of ordinary skill in the art and will vary to some extent depending upon the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, “about” will mean up to plus or minus 10% of the particular term. For example, in some embodiments, it will mean plus or minus 5% of the particular term. Certain ranges are presented herein with numerical values being preceded by the term “about.” The term “about” is used herein to provide literal support for the exact number that it precedes, as well as a number that is near to or approximately the number that the term precedes. In determining whether a number is near to or approximately a specifically recited number, the near or approximating unrecited number may be a number, which, in the context in which it is presented, provides the substantial equivalent of the specifically recited number.

**[00305]** Ranges can be expressed herein as from “about” one particular value, and / or to “about” another particular value. When such a range is expressed, another case includes from the

one particular value and / or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms another case. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. As described herein, any concentration range, percentage range, ratio range or integer range is to be understood to be inclusive of the value of any integer within the recited range and, when appropriate, fractions thereof (such as one-tenth and one-hundredth of an integer), unless otherwise indicated.

**[00306]** Units, prefixes, and symbols used herein are provided using their Systeme International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range.

**[00307]** The terms “at least”, “more than”, “or more”, and the like, *e.g.*, “at least one” are understood to include but not be limited to at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149 or 150, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000 or more than the stated value. Also included is any greater number or fraction in between. Conversely, the term “no more than” includes each value less than the stated value. For example, “no more than 100 nucleotides” includes 100, 99, 98, 97, 96, 95, 94, 93, 92, 91, 90, 89, 88, 87, 86, 85, 84, 83, 82, 81, 80, 79, 78, 77, 76, 75, 74, 73, 72, 71, 70, 69, 68, 67, 66, 65, 64, 63, 62, 61, 60, 59, 58, 57, 56, 55, 54, 53, 52, 51, 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, and 0 nucleotides. Also included is any lesser number or fraction in between. The terms “plurality”, “at least two”, “two or more”, “at least second”, and the like, are understood to include but not limited to at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,

26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149 or 150, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000 or more. Also included is any greater number or fraction in between.

**[00308]** “Administration” as it applies to an animal, human, experimental subject, cell, tissue, organ, or biological fluid, refers to contact of an exogenous pharmaceutical, therapeutic, diagnostic agent, or composition to the animal, human, subject, cell, tissue, organ, or biological fluid. Treatment of a cell encompasses contact of a reagent to the cell, as well as contact of a reagent to a fluid, where the fluid is in contact with the cell. The term “subject” or “patient” refers to any single subject for which therapy is desired or that is participating in a clinical trial, epidemiological study or used as a control, and includes any organism, preferably an animal, more preferably a mammal (*e.g.*, rat, mouse, dog, cat, horse, cattle), and most preferably a human.

**[00309]** The term “anti-cancer agent” as used herein refers to any agent that can be used to treat a cell proliferative disorder such as cancer, including but not limited to, cytotoxic agents, chemotherapeutic agents, radiotherapy and radiotherapeutic agents, targeted anti-cancer agents, and immunotherapeutic agents, including cellular therapies.

**[00310]** Antibodies are large, complex molecules (molecular weight of ~150,000 or about 1320 amino acids) with intricate internal structure. The term “antibody” (Ab) includes, without limitation, a glycoprotein immunoglobulin which binds specifically to an antigen. In general, antibodies are large, complex molecules (molecular weight of ~150,000 or about 1320 amino acids) with an intricate internal structure. An antibody can comprise at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds, or an antigen-binding molecule thereof. Each H chain comprises a heavy chain variable region (abbreviated herein as HCVR or VH or Vh) and a heavy chain constant region. The heavy chain constant region



comprises three constant domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or VL or VI) and a light chain constant region. The term “antibody” as used herein refers to a polypeptide of the immunoglobulin family that can bind a corresponding antigen non-covalently, reversibly, and in a specific manner.

**[00311]** The light and heavy chain variable regions come together in 3-dimensional space to form a variable region that binds the antigen (for example, a receptor on the surface of a cell). The variable regions of each light/heavy chain (VI/Vh) pair form the antibody binding site. In general, an intact antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are, generally, the same in primary sequence.

**[00312]** As will be presented in more detail below, within each light or heavy chain variable region, there are three short segments (averaging 10 amino acids in length) called the complementarity determining regions (“CDRs”). The six CDRs in an antibody variable domain (three from the light chain and three from the heavy chain) fold up together in 3-dimensional space to form the actual antibody binding site which docks onto the target antigen. The terms “CDR-L1,” “CDR-L2” and “CDR-L3” as provided herein refer to the complementarity determining regions (CDR) 1, 2, and 3 of the variable light (L) chain of an antibody. In embodiments, the variable light chain provided herein includes in N-terminal to C-terminal direction a CDR-L1, a CDR-L2 and a CDR-L3. Likewise, the terms “CDR-H1,” “CDR-H2” and “CDR-H3” as provided herein refer to the complementarity determining regions (CDR) 1, 2, and 3 of the variable heavy (H) chain of an antibody. In certain embodiments, the variable heavy chain provided herein includes in N-terminal to C-terminal direction a CDR-H1, a CDR-H2 and a CDR-H3. As detailed further below, the position and length of the CDRs have been precisely defined by Kabat, E. et al., Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services, 1983, 1987. Naturally-produced antibodies are also glycosylated, *e.g.*, on the CH2 domain.

**[00313]** The part of a variable region not contained in the CDRs is called the framework (“FR”), which forms the environment for the CDRs. Thus, the complementarity determining regions (CDRs) are interspersed with regions that are more conserved, *i.e.*, the framework regions. Accordingly, each VH and VL comprises three CDRs and four FRs, arranged from

amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. While the variable regions of the heavy and light chains contain the binding domain that interacts with an antigen, the constant regions of the antibody may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system.

**Table 7: CDR Numbering:**

| Loop | Kabat               | AbM       | Chothia           | Contact   |
|------|---------------------|-----------|-------------------|-----------|
| L1   | L24--L34            | L24--L34  | L24--L34          | L30--L36  |
| L2   | L50--L56            | L50--L56  | L50--L56          | L46--L55  |
| L3   | L89--L97            | L89--L97  | L89--L97          | L89--L96  |
| H1   | H31--H35B           | H26--H35B | H26--H32 . . . 34 | H30--H35B |
|      | (Kabat Numbering)   |           |                   |           |
| H1   | H31--H35            | H26--H35  | H26--H32          | H30--H35  |
|      | (Chothia Numbering) |           |                   |           |
| H2   | H50--H65            | H50--H58  | H52--H56          | H47--H58  |
| H3   | H95--H102           | H95--H102 | H95--H102         | H93--H101 |

**[00314]** A number of definitions of the CDRs are commonly in use: Kabat numbering, Chothia numbering, AbM numbering, or contact numbering. The AbM definition is a compromise between the two used by Oxford Molecular's AbM antibody modelling software. The contact definition is based on an analysis of the available complex crystal structures.

**[00315]** The positions of the CDRs and framework regions can be determined using various definitions well known in the art, *e.g.*, Kabat, Chothia, AbM and IMGT (see, *e.g.*, Johnson et al., *Nucleic Acids Res.*, 29:205-206 (2001); Chothia and Lesk, *J. Mol. Biol.*, 196:901-917 (1987); Chothia et al., *Nature*, 342:877-883 (1989); Chothia et al., *J. Mol. Biol.*, 227:799-817 (1992); Al-Lazikani et al., *J. Mol. Biol.*, 273:927-748 (1997) ImMunoGenTics (IMGT) numbering (Lefranc, M.-P., *The Immunologist*, 7, 132-136 (1999); Lefranc, M.P. et al., *Dev. Comp. Immunol.*, 27, 55-77 (2003) ("IMGT" numbering scheme)). Definitions of antigen combining sites are also described in the following: Ruiz et al., *Nucleic Acids Res.*, 28:219-221 (2000); and Lefranc, M. P., *Nucleic Acids Res.*, 29:207-209 (2001); MacCallum et al., *J. Mol. Biol.*, 262:732-745 (1996);

and Martin et al., Proc. Natl. Acad. Sci. USA, 86:9268-9272 (1989); Martin et al., Methods Enzymol., 203:121-153 (1991); and Rees et al., In Sternberg M. J. E. (ed.), Protein Structure Prediction, Oxford University Press, Oxford, 141-172 (1996).

**[00316]** For example, under Kabat, the CDR amino acid residues in the heavy chain variable domain (VH) are numbered 31-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3); and the CDR amino acid residues in the light chain variable domain (VL) are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3). Under Chothia, the CDR amino acids in the VH are numbered 26-32 (HCDR1), 52-56 (HCDR2), and 95-102 (HCDR3); and the amino acid residues in VL are numbered 26-32 (LCDR1), 50-52 (LCDR2), and 91-96 (LCDR3). By combining the CDR definitions of both Kabat and Chothia, the CDRs consist of amino acid residues 26-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3) in human VH and amino acid residues 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3) in human VL. Under IMGT, the CDR amino acid residues in the VH are numbered approximately 26-35 (HCDR1), 51-57 (HCDR2) and 93-102 (HCDR3), and the CDR amino acid residues in the VL are numbered approximately 27-32 (LCDR1), 50-52 (LCDR2), and 89-97 (LCDR3) (numbering according to Kabat). Under IMGT, the CDR regions of an antibody can be determined using the program IMGT/DomainGapAlign.

**[00317]** In certain aspects, the CDRs of an antibody can be determined according to the Chothia numbering scheme, which refers to the location of immunoglobulin structural loops (see, e.g., Chothia C. & Lesk A.M., (1987), J Mol Biol 196: 901-917; Al-Lazikani B. et al., (1997) J Mol Biol 273: 927-948; Chothia C. et al., (1992) J Mol Biol 227: 799-817; Tramontano A. et al., (1990) J Mol Biol 215(1): 175-82; and U.S. Pat. No. 7,709,226). Typically, when using the Kabat numbering convention, the Chothia CDR-H1 loop is present at heavy chain amino acids 26 to 32, 33, or 34, the Chothia CDR-H2 loop is present at heavy chain amino acids 52 to 56, and the Chothia CDR-H3 loop is present at heavy chain amino acids 95 to 102, while the Chothia CDR-L1 loop is present at light chain amino acids 24 to 34, the Chothia CDR-L2 loop is present at light chain amino acids 50 to 56, and the Chothia CDR-L3 loop is present at light chain amino acids 89 to 97. The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is

present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34). In a specific embodiment, the CDRs of the antibodies described herein have been determined according to the Chothia numbering scheme.

**[00318]** When an antibody is said to comprise CDRs by a certain definition of CDRs (*e.g.*, Kabat) that definition specifies the minimum number of CDR residues present in the antibody (*i.e.*, the Kabat CDRs). It does not exclude the fact that other residues falling within another conventional CDR definition but outside the specified definition are also present. For example, an antibody comprising CDRs defined by Kabat includes among other possibilities, an antibody in which the CDRs contain Kabat CDR residues and no other CDR residues, and an antibody in which HCDR1 is a composite Chothia-Kabat HCDR1 and other CDRs contain Kabat CDR residues and no additional CDR residues based on other definitions.

**[00319]** In some instances, a CDR is substantially identical to one found in a reference antibody (*e.g.*, an antibody of the present disclosure) and/or the sequence of a CDR provided in the present disclosure. In some embodiments, a CDR is substantially identical to a reference CDR (*e.g.*, a CDR provided in the present disclosure) in that it is either identical in sequence or contains between 1, 2, 3, 4, or 5 (*e.g.*, 1-5) amino acid substitutions as compared with the reference CDR. In some embodiments a CDR is substantially identical to a reference CDR in that it shows at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the reference CDR (*e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%). In some embodiments a CDR is substantially identical to a reference CDR in that it shows at least 96%, 96%, 97%, 98%, 99%, or 100% sequence identity with the reference CDR. In some embodiments a CDR is substantially identical to a reference CDR in that one amino acid within the CDR is deleted, added, or substituted as compared with the reference CDR while the CDR has an amino acid sequence that is otherwise identical with that of the reference CDR. In some embodiments a CDR is substantially identical to a reference CDR in that 2, 3, 4, or 5 (*e.g.*, 2-5) amino acids within the CDR are deleted, added, or substituted as compared with the reference CDR while the CDR has an amino acid sequence that is otherwise identical to the reference CDR. In various embodiments, an antigen binding fragment binds a same antigen as a reference antibody.

[00320] The term “antibody” further includes, but is not limited to, monoclonal antibodies, human antibodies, humanized antibodies, chimeric antibodies, and anti-idiotypic (anti-Id) antibodies. Antibodies can include, for example, monoclonal antibodies, recombinantly produced antibodies, monospecific antibodies, multispecific antibodies (including bispecific antibodies), human antibodies, engineered antibodies, humanized antibodies, chimeric antibodies, immunoglobulins, synthetic antibodies, tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, an antibody heavy chain monomer, an antibody light chain dimer, an antibody heavy chain dimer, an antibody light chain-antibody heavy chain pair, intrabodies, antibody fusions (sometimes referred to herein as “antibody conjugates”), heteroconjugate antibodies, single domain antibodies, monovalent antibodies, single chain antibodies or single-chain Fvs (scFv), camelized antibodies, affibodies, Fab fragments, F(ab')<sub>2</sub> fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-anti-Id antibodies), minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as “antibody mimetics”), and antigen binding fragments of any of the above. In certain embodiments, antibodies described herein refer to polyclonal antibody populations. Antibodies may also comprise, for example, Fab' fragments, Fd' fragments, Fd fragments, isolated CDRs, single chain Fvs, polypeptide-Fc fusions, single domain antibodies (*e.g.*, shark single domain antibodies such as IgNAR or fragments thereof), camelid antibodies, single chain or Tandem diabodies (TandAb®), Anticalins®, Nanobodies® minibodies, BiTE®, ankyrin repeat proteins or DARPINs®, Avimers®, DARTs, TCR-like antibodies, Adnectins®, Affilins®, Trans-Bodies®, Affibodies®, TrimerX®, MicroProteins, Fynomers®, Centyrins®, and KALBITOR®s.

[00321] An immunoglobulin may derive from any of the commonly known isotypes, including but not limited to IgA, secretory IgA, IgG, IgE, IgM, IgD, IgA and IgY. IgG subclasses are also well known to those in the art and include but are not limited to human IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The term “antibody” and “immunoglobulin” or “Ig” may be used interchangeably herein.

[00322] The term “antibody” includes intact antibodies and binding fragments thereof. Typically, fragments compete with the intact antibody from which they were derived for specific

binding to the target. Fragments include separate heavy chains, light chain Fab, Fab', F(ab')<sub>2</sub>, Fv fragments and single domain antibodies. Single (variable) domain antibodies include VH regions separated from their VL partners (or vice versa) in conventional antibodies (Ward et al., 1989, Nature 341: 544-546) as well as VH regions (sometimes known as VHH) from species such as Camelidae or cartilaginous fish (*e.g.*, a nurse shark) in which VH regions are not associated with VL regions (see, *e.g.*, WO 9404678). For example, natural single variable region antibodies from Camelidae include a VHH variable region, and CH2 and CH3 constant regions. Single domain antibodies can be subject to humanization by analogous approaches to conventional antibodies. The Dabs type of antibodies are usually obtained from antibodies of human origin. Nanobody types of antibodies are of Camelidae or shark origin and can be subject to humanization. Fragments can be produced by recombinant DNA techniques, or by enzymatic or chemical separation of intact immunoglobulins. The term "antibody" also includes bi-, tri- and multi-specific antibodies. For example, a bispecific or bifunctional antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites (see, *e.g.*, Songsivilai and Lachmann, Clin. Exp. Immunol., 79:315-321 (1990); Kostelny et al., J. Immunol., 148:1547-53 (1992)).

[00323] Antibodies can exist, *e.g.*, as intact immunoglobulins or as a number of well-characterized fragments produced by digestion with various peptidases. For example, pepsin digests an antibody below the disulfide linkages in the hinge region to produce F(ab')<sub>2</sub>, a dimer of Fab which itself is a light chain joined to VH-CH1 by a disulfide bond. The F(ab')<sub>2</sub> may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the F(ab')<sub>2</sub> dimer into an Fab' monomer. The Fab' monomer is essentially Fab with part of the hinge region (see Fundamental Immunology (Paul ed., 3d ed. 1993). While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such fragments may be synthesized *de novo* either chemically or by using recombinant DNA methodology. Thus, the term antibody, as used herein, also includes antibody fragments either produced by the modification of whole antibodies, or those synthesized *de novo* using recombinant DNA methodologies (*e.g.*, single chain Fv) or those identified using phage display libraries (see, *e.g.*, McCafferty et al. (1990)).

[00324] An “antigen binding molecule,” “antigen binding portion,” or “antibody fragment” refers to any molecule that comprises the antigen binding parts (*e.g.*, CDRs) of the antibody from which the molecule is derived. Examples of antibody fragments include, but are not limited to, Fab, Fab', F(ab')<sub>2</sub>, and Fv fragments, dAb, linear antibodies, scFv antibodies, and multispecific antibodies formed from antigen binding molecules. Peptibodies (*i.e.*, Fc fusion molecules comprising peptide binding domains) are another example of suitable antigen binding molecules. In some embodiments, the antigen binding molecule binds to an antigen on a tumor cell. In certain embodiments, the antigen binding molecule binds to PD-1. In further embodiments, the antigen binding molecule is an antibody fragment that specifically binds to the antigen, including one or more of the complementarity determining regions (CDRs) thereof. In further embodiments, the antigen binding molecule is a single chain variable fragment (scFv).

[00325] Unless otherwise indicated, an “antigen-binding fragment” means antigen-binding fragments of antibodies, *i.e.*, antibody fragments that retain the ability to bind specifically to the antigen bound by the full-length antibody, *e.g.*, fragments that retain one or more CDR regions. Examples of antigen-binding fragments include, but not limited to, Fab, Fab', F(ab')<sub>2</sub>, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules, *e.g.*, single chain Fv (ScFv); nanobodies and multi-specific antibodies formed from antibody fragments. In some embodiments, the antigen binding molecule binds to an antigen on a tumor cell. In certain embodiments, the antigen binding molecule binds to PD-1.

[00326] An antigen binding fragment may be produced by any means. For example, in some embodiments, an antigen binding fragment may be enzymatically or chemically produced by fragmentation of an intact antibody. In some embodiments, an antigen binding fragment may be recombinantly produced (*i.e.*, by expression of an engineered nucleic acid sequence. In some embodiments, an antigen binding fragment may be wholly or partially synthetically produced. In some embodiments, an antigen binding fragment may have a length of at least about 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190 amino acids or more; in some embodiments at least about 200 amino acids (*e.g.*, 50-100, 50-150, 50-200, or 100-200 amino acids).

[00327] An “anti-tumor effect” as used herein, refers to a biological effect that can present as

a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in tumor cell proliferation, a decrease in the number of metastases, an increase in overall or progression-free survival, an increase in life expectancy, or amelioration of various physiological symptoms associated with the tumor.

**[00328]** “Anti-tumor response” when referring to a cancer patient treated with a therapeutic regimen, such as a therapy described herein, means at least one positive therapeutic effect, such as for example, reduced number of cancer cells, reduced tumor size, reduced rate of cancer cell infiltration into peripheral organs, reduced rate of tumor metastasis or tumor growth, or progression-free survival. Positive therapeutic effects in cancer can be measured in a number of ways (See, *e.g.*, Weber, W.A. “Assessing tumor response to therapy.” *Journal of nuclear medicine* 50.Suppl 1 (2009): 1S-10S); Eisenhauer et al., *supra*). In some embodiments, an anti-tumor response to a therapy described herein is assessed using RECIST 1.1 criteria, bidimensional irRC or unidimensional irRC. In some embodiments, an anti-tumor response is any of SD, PR, CR, PFS, or DFS.

**[00329]** As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a “conservatively modified variant” where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles.

**[00330]** The most commonly occurring exchanges are isoleucine/valine, tyrosine/phenylalanine, aspartic acid/glutamic acid, lysine/arginine, methionine/leucine, aspartic acid/asparagine, glutamic acid/glutamine, leucine/isoleucine, methionine/isoleucine, threonine/serine, tryptophan/phenylalanine, tyrosine/histidine, tyrosine/tryptophan, glutamine/arginine, histidine/asparagine, histidine/glutamine, lysine/asparagine, lysine/glutamine, lysine/glutamic acid, phenylalanine/leucine, phenylalanine/methionine, serine/alanine, serine/asparagine, valine/leucine, and valine/methionine. The following eight groups each contain exemplary amino acids that may be considered conservative substitutions for one another (see, *e.g.*, Creighton, *Proteins* (1984)).



- 1) Alanine (A), Glycine (G);
- 2) Aspartic acid (D), Glutamic acid (E);
- 3) Asparagine (N), Glutamine (Q);
- 4) Arginine (R), Lysine (K);
- 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V);
- 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W);
- 7) Serine (S), Threonine (T); and
- 8) Cysteine (C), Methionine (M).

**Individual Exemplary Conservative Amino Acid Substitutions:**

| Table 8          |                           |
|------------------|---------------------------|
| Original residue | Conservative substitution |
| Ala (A)          | Gly; Ser                  |
| Arg (R)          | Lys, His                  |
| Asn (N)          | Gln; His                  |
| Asp (D)          | Glu; Asn                  |
| Cys (C)          | Ser; Ala                  |
| Gln (Q)          | Asn                       |
| Glu (E)          | Asp; Gln                  |
| Gly (G)          | Ala                       |
| His (H)          | Asn; Gln                  |
| Ile (I)          | Leu; Val                  |
| Leu (L)          | Ile; Val                  |
| Lys (K)          | Arg; His                  |
| Met (M)          | Leu; Ile; Tyr             |
| Phe (F)          | Tyr; Met; Leu             |
| Pro (P)          | Ala                       |
| Ser (S)          | Thr                       |
| Thr(T)           | Ser                       |
| Trp (W)          | Tyr; Phe                  |
| Tyr (Y)          | Trp; Phe                  |

| Table 8          |                           |
|------------------|---------------------------|
| Original residue | Conservative substitution |
| Val (V)          | Ile; Leu                  |

[00331] In some embodiments, there may be at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, or at least 40 conservative substitutions. In some embodiments, there may be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 conservative substitutions. Thus, a “conservative amino acid substitution” refers to substitutions of amino acids in a protein with other amino acids having similar characteristics (*e.g.*, charge, side-chain size, hydrophobicity/hydrophilicity, backbone conformation and rigidity, etc.) such that the changes can frequently be made without altering the biological activity or other desired property of the protein, such as antigen affinity and/ or specificity. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, *e.g.*, Watson et al. (1987) *Molecular Biology of the Gene*, The Benjamin/Cummings Pub. Co., p. 224 (4th Ed.)). In addition, substitutions of structurally or functionally similar amino acids are less likely to disrupt biological activity.

[00332] The term “buffer” encompasses those agents which maintain the solution pH of the compositions of the present disclosure in an acceptable range.

[00333] “Chemotherapeutic agent” refers to a chemical or biological substance that can cause death of cancer cells, or interfere with growth, division, repair, and/or function of cancer cells. Classes of chemotherapeutic agents include, but are not limited to: microtubule inhibitors, *e.g.*, taxanes (paclitaxel, docetaxel), and vinca alkaloids (vincristine, vinblastine, vinorelbine); antimetabolites (5-fluorouracil, capecitabine, gemcitabine), and antifolates (methotrexate, pemetrexed); kinase inhibitors (crizotinib, erlotinib, sunitinib); topoisomerase inhibitors (deruxtecan, topotecan, irinotecan, anthracyclines, etoposide); cell-cycle independent drugs, *e.g.*,

platinum compounds and analogues (oxaliplatin), triazenes, alkylating agents (cyclophosphamide), spindle poison plant alkaloids (doxorubicin), cytotoxic/antitumor antibiotics (bleomycin, mithramycin, mitomycin), photosensitizers, anti-estrogens and selective estrogen receptor modulators (SERMs), anti-progesterones, estrogen receptor down-regulators (ERDs), estrogen receptor antagonists, luteinizing hormone-releasing hormone agonists, anti-androgens, aromatase inhibitors, EGFR inhibitors, VEGF inhibitors, and anti-sense oligonucleotides that inhibit expression of genes implicated in abnormal cell proliferation or tumor growth. Current standard of care (SOC) treatments for certain cancers, such as colon, in the early-line setting include chemotherapy based on fluoropyrimidine, oxaliplatin, and irinotecan used in combination or sequentially, with option for monoclonal antibodies targeting vascular endothelial growth factor (VEGF) (*e.g.*, bevacizumab, ziv-aflibercept) or its receptors (*e.g.*, ramucirumab), and in patients with Ras wild type tumors, monoclonal antibodies targeting the epidermal growth factor (EGF) receptor (*e.g.*, cetuximab, panitumumab). Treatment options for heavily pre-treated patients beyond the second-line setting are especially limited and associated toxicities can be severe.

**[00334]** “Co-administration” as used herein for agents such as the disclosed anti-PD-1 antibody, *e.g.*, Tislelizumab, and a chemotherapeutic drug, means that the agents are administered so as to have overlapping therapeutic activities, and not necessarily that the agents are administered simultaneously to the subject. The agents may or may not be in physical combination prior to administration. In an embodiment, the agents are administered to a subject simultaneously or at about the same time. For example, the agents may be contained in separate vials, when in liquid solution, may be mixed into the same intravenous infusion bag or injection device, and administered simultaneously to the patient.

**[00335]** “Combination therapy” refers to those situations in which a subject is simultaneously exposed to two or more therapeutic regimens (*e.g.*, two or more therapeutic moieties). In some embodiments, the two or more regimens may be administered simultaneously; in some embodiments, such regimens may be administered sequentially (*e.g.*, all “doses” of a first regimen are administered prior to administration of any doses of a second regimen); in some embodiments, such agents are administered in overlapping dosing regimens. In some

embodiments, “administration” of combination therapy may involve administration of one or more agent(s) or modality(ies) to a subject receiving the other agent(s) or modality(ies) in the combination. For clarity, combination therapy does not require that individual agents be administered together in a single composition (or even necessarily at the same time), although in some embodiments, two or more agents, or active moieties thereof, may be administered together in a combination composition, or even in a combination compound (*e.g.*, as part of a single chemical complex or covalent entity). Such administration also encompasses co-administration in multiple, or in separate containers (*e.g.*, capsules, powders, and liquids) for each active ingredient. Powders and/or liquids can be reconstituted or diluted to a desired dose prior to administration. Thus, the phrase “in combination with” means that an anti-PD-1 antibody is administered to a subject at the same time as, just before, or just after administration of an additional therapeutic agent. In certain embodiments, an anti-PD-1 antibody is administered as a co-formulation with an additional therapeutic agent.

[00336] Throughout the specification the word “comprising,” or variations such as “comprises” or “comprising,” will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps. It is understood that wherever aspects are described herein with the language “comprising,” otherwise analogous aspects described in terms of “consisting of” and/or “consisting essentially of” are also provided.

[00337] The terms “constant region” and “constant domain” are interchangeable and have a meaning common in the art. The constant region is an antibody portion, *e.g.*, a carboxyl terminal portion of a light and/or heavy chain which is not directly involved in binding of an antibody to an antigen but which can exhibit various effector functions, such as interaction with the Fc receptor. The constant region of an immunoglobulin molecule generally has a more conserved amino acid sequence relative to an immunoglobulin variable domain.

[00338] “Conservatively modified variants” or “conservative substitution” refers to substitutions of amino acids in a protein with other amino acids having similar characteristics (*e.g.*, charge, side-chain size, hydrophobicity/hydrophilicity, backbone conformation and rigidity, etc.) such that the changes can frequently be made without altering the biological

activity or other desired property of the protein, such as antigen affinity and/or specificity. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, *e.g.*, Watson et al. (1987) *Molecular Biology of the Gene*, The Benjamin/Cummings Pub. Co., p. 224 (4th Ed.)). In addition, substitutions of structurally or functionally similar amino acids are less likely to disrupt biological activity. Exemplary conservative substitutions are set forth herein.

**[00339]** The term “dosage form” may be used to refer to a physically discrete unit of an active agent (*e.g.*, an antigen binding system or antibody) for administration to a subject. Generally, each such unit contains a predetermined quantity of active agent. In some embodiments, such quantity is a unit dosage amount (or a whole fraction thereof) appropriate for administration in accordance with a dosing regimen that has been determined to correlate with a desired or beneficial outcome when administered to a relevant population. The total amount of a therapeutic composition or agent administered to a subject is determined by one or more medical practitioners and may involve administration of more than one dosage forms.

**[00340]** The term “dosing regimen” may be used to refer to a set of one or more unit doses that are administered individually to a subject. In some embodiments, a given therapeutic agent has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which is separated in time from other doses. In some embodiments, a dosing regimen comprises a plurality of doses and consecutive doses are separated from one another by time periods of equal length; in some embodiments, a dosing regimen comprises a plurality of doses and consecutive doses are separated from one another by time periods of at least two different lengths. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from the first dose amount. In some embodiments, a dosing regimen is periodically adjusted to achieve a desired or beneficial outcome.

**[00341]** A “Durable Stable Disease Rate” means stable disease (SD) for ~23 weeks, where SD

is cancer that is neither decreasing nor increasing in extent or severity.

[00342] “Effector cell” refers to a cell of the immune system that expresses one or more Fc receptors and mediates one or more effector functions. In some embodiments, effector cells may comprise, without limitation, one or more of monocytes, macrophages, neutrophils, dendritic cells, eosinophils, mast cells, platelets, large granular lymphocytes, Langerhans’ cells, natural killer (NK) cells, T-lymphocytes, and B-lymphocytes. Effector cells may be of any organism comprising, without limitation, humans, mice, rats, rabbits, and monkeys.

[00343] “Effector function” refers to a biological result of interaction of an antibody Fc region with an Fc receptor or ligand. Effector functions comprise, without limitation, antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), and complement-mediated cytotoxicity (CMC). An effector function may be antigen binding dependent, antigen binding independent, or both. ADCC refers to lysis of antibody-bound target cells by immune effector cells. Without wishing to be bound by any theory, ADCC is generally understood to involve Fc receptor (FcR)-bearing effector cells recognizing and subsequently killing antibody-coated target cells (*e.g.*, cells that express on their surface antigens to which an antibody is bound). Effector cells that mediate ADCC may comprise immune cells, comprising yet not limited to, one or more of natural killer (NK) cells, macrophages, neutrophils, eosinophils.

[00344] The term “excipient” refers to an agent that may be comprised in a composition, for example to provide or contribute to a desired consistency or stabilizing effect. In some embodiments, a suitable excipient may comprise, for example, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol, or the like.

[00345] The term “heavy chain” when used in reference to an antibody can refer to any distinct type, *e.g.*, alpha ( $\alpha$ ), delta ( $\delta$ ), epsilon ( $\epsilon$ ),  $\gamma$  ( $\gamma$ ) and mu ( $\mu$ ), based on the amino acid sequence of the constant domain, which give rise to IgA, IgD, IgE, IgG and IgM classes of antibodies, respectively, including subclasses of IgG, *e.g.*, IgG1, IgG2, IgG3 and IgG4.

[00346] As used herein, a “host cell” refers to any cell of any organism that is used for the

purpose of producing a recombinant protein encoded by an expression vector or propagating the expression vector introduced into the host cell. A “mammalian recombinant host cell” refers to a mammalian host cell that comprises a heterologous expression vector, which may or may not be integrated into the host cell chromosome. A “bacterial recombinant host cell” refers to a bacterial host cell that comprises a heterologous expression vector, which may or may not be integrated into the host cell chromosome.

[00347] The term “human antibody” herein means an antibody that comprises human immunoglobulin protein sequences only. The variable and constant domain sequences generated may be assembled, or derived from human immunoglobulin sequences, or sequences indistinguishable therefrom. A human antibody can contain murine carbohydrate chains if produced in a mouse, in a mouse cell, or in a hybridoma derived from a mouse cell. Similarly, “mouse antibody” or “rat antibody” mean an antibody that comprises only mouse or rat immunoglobulin protein sequences, respectively.

[00348] In some embodiments, antibodies (or antibody components) may be considered to be “human” even though their amino acid sequences comprise residues or elements not encoded by human germline immunoglobulin sequences (*e.g.*, variations introduced by *in vitro* random or site-specific mutagenesis or introduced by *in vivo* somatic mutation).

[00349] The term “humanized” or “humanized antibody” means forms of antibodies that contain sequences from non-human (*e.g.*, murine) antibodies as well as human antibodies. Such antibodies contain minimal sequence derived from non-human immunoglobulin. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. The prefix “hum,” “hu,” “Hu,” or “h” is added to antibody clone designations when necessary to distinguish humanized antibodies from parental rodent antibodies. The humanized forms of rodent antibodies will generally comprise the same CDR sequences of the parental rodent antibodies, although certain amino acid substitutions can be included to increase affinity,

increase stability of the humanized antibody, remove a post-translational modification or for other reasons. In some embodiments, a “humanized” antibody comprises one or more framework domains having substantially the amino acid sequence of a human framework domain, and one or more complementary determining regions having substantially the amino acid sequence as that of a non-human antibody. In some embodiments, a humanized antibody comprises at least a portion of an immunoglobulin constant region (Fc), generally that of a human immunoglobulin constant domain. In some embodiments, a humanized antibody may comprise a CH1, hinge, CH2, CH3, and, optionally, a CH4 region of a human heavy chain constant domain.

[00350] A “hybridoma” producing a monoclonal antibody can be cultivated in vitro or in vivo. High titers of monoclonal antibodies can be obtained in in vivo production where cells from the individual hybridomas are injected intraperitoneally into mice, such as pristine-primed Balb/c mice to produce ascites fluid containing high concentrations of the desired antibodies. Monoclonal antibodies of isotype IgM or IgG can be purified from such ascites fluids, or from culture supernatants, using column chromatography methods well known to those of skill in the art.

[00351] The term “hypervariable region” means the amino acid residues of an antibody that are responsible for antigen-binding. The hypervariable region comprises amino acid residues from a “complementarity determining region” or “CDR” (*i.e.*, CDR-L1, CDR-L2 and CDR-L3 in the light chain variable domain and CDR-H1, CDR-H2 and CDR-H3 in the heavy chain variable domain). See, Kabat et al. (1991) Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (defining the CDR regions of an antibody by sequence); see also Chothia and Lesk (1987) J. Mol. Biol. 196: 901-917 (defining the CDR regions of an antibody by structure). The term “framework” or “FR” means those variable domain residues other than the hypervariable region residues defined herein as CDR residues.

[00352] Typically, the variable domains of both the heavy and light chains comprise three hypervariable regions, also called “complementarity determining regions (CDRs)”, which are located between relatively conserved framework regions (FR). The CDRs are usually aligned by the framework regions, enabling binding to a specific epitope. In general, from N-terminal to C-



terminal, both light and heavy chain variable domains comprise FR-1 (or FR1), CDR-1 (or CDR1), FR-2 (FR2), CDR-2 (CDR2), FR-3 (or FR3), CDR-3 (CDR3), and FR-4 (or FR4). The assignment of amino acids to each domain is, generally, in accordance with the definitions of Sequences of Proteins of Immunological Interest, Kabat, et al., National Institutes of Health, Bethesda, Md. ; 5<sup>th</sup> ed.; NIH Publ. No. 91-3242 (1991); Kabat (1978) Adv. Prot. Chem. 32: 1-75; Kabat, et al., (1977) J. Biol. Chem. 252:6609-6616; Chothia, et al, (1987) J Mol. Biol. 196:901-917 or Chothia, et al, (1989) Nature 342:878-883.

**[00353]** The term “identity” refers to the overall relatedness between polymeric molecules, *e.g.*, between nucleic acid molecules (*e.g.*, DNA molecules and/or RNA molecules) and/or between polypeptide molecules. The term “identical” or “percent identity” is a numeric score determined for a pair of aligned amino acid or nucleic acid sequences. Percent identity measures the number of identical residues (“identity”) between two sequences in relation to the length of the alignment across a “comparison window.” The number shows the % of amino acid residues or nucleotides that are the same between two sequences and indicates the degree of primary structure similarity.

**[00354]** Methods for the calculation of a percent identity as between two provided polypeptide sequences are known. Calculation of the percent identity of two nucleic acid or polypeptide sequences, for example, may be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps may be introduced in one or both of a first and a second sequences for optimal alignment and non-identical sequences may be disregarded for comparison purposes). The nucleotides or amino acids at corresponding positions are then compared. When a position in the first sequence is occupied by the same residue (*e.g.*, nucleotide or amino acid) as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, optionally considering the number of gaps, and the length of each gap, which may need to be introduced for optimal alignment of the two sequences. Comparison or alignment of sequences and determination of percent identity between two sequences may be accomplished using a mathematical algorithm, such as BLAST (basic local alignment search tool). In some embodiments, polymeric molecules are considered to be

“homologous” to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical (*e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%).

**[00355]** To calculate percent identity, the sequences being compared are typically aligned in a way that gives the largest match between the sequences. For sequence comparison, generally one sequence acts as a reference sequence, to which test sequences may be compared. When using a sequence comparison algorithm, test and reference sequences may be entered into a computer, subsequent coordinates may be designated, if necessary, and sequence algorithm program parameters may be designated. A polypeptide may be considered to be identical or substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Methods of alignment of sequences for comparison are well-known in the art.

**[00356]** One example of a computer program that can be used to determine percent identity is the GCG program package, which includes GAP (Devereux et al., 1984, Nucl. Acid Res. 12:387; Genetics Computer Group, University of Wisconsin, Madison, Wis.). The computer algorithm GAP is used to align the two polypeptides or polynucleotides for which the percent sequence identity is to be determined. The sequences are aligned for optimal matching of their respective amino acid or nucleotide (the “matched span,” as determined by the algorithm). In certain embodiments, a standard comparison matrix (see, Dayhoff et al., 1978, Atlas of Protein Sequence and Structure 5:345-352 for the PAM 250 comparison matrix; Henikoff et al., 1992, Proc. Natl. Acad. Sci. U.S.A. 89:10915-10919 for the BLOSUM 62 comparison matrix) is also used by the algorithm. Other algorithms are also available for comparison of amino acid or nucleic acid sequences, comprising those available in commercial computer programs such as BLASTN for nucleotide sequences and BLASTP, gapped BLAST, and PSI-BLAST for amino acid sequences. Exemplary such programs are described in Altschul et al., “Basic local alignment search tool,” J. Mol. Biol., 215(3): 403-410, 1990; Altschul et al., Methods in Enzymology; Altschul et al., “Gapped BLAST and PSI-BLAST: a new generation of protein database search programs,” Nucleic Acids Res. 25:3389-3402, 1997; Baxevanis et al., Bioinformatics: A Practical Guide to the Analysis of Genes and Proteins, Wiley, 1998; and Misener et al., (eds.),

Bioinformatics Methods and Protocols (Methods in Molecular Biology, Vol. 132), Humana Press, 1999.

**[00357]** In addition to identifying similar sequences, the programs mentioned above generally provide an indication of the degree of similarity. In some embodiments, two sequences are considered to be substantially similar if at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or more of their corresponding residues are similar and/or identical over a relevant stretch of residues (*e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%). In some embodiments, the relevant stretch is a complete sequence. In some embodiments, the relevant stretch is at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 95, at least 100, at least 125, at least 150, at least 175, at least 200, at least 225, at least 250, at least 275, at least 300, at least 325, at least 350, at least 375, at least 400, at least 425, at least 450, at least 475, at least 500 or more residues. Sequences with substantial sequence similarity may be homologs of one another.

**[00358]** Positive therapeutic effects in cancer can be measured in a number of ways (See, W. A Weber, J Nucl. Med. 50: I S-10S (2009)). One common measure of efficacy is the T/C ratio, which is the ratio of tumor volume in control versus treated subjects at a specified time, where  $T/C (\%) = \text{Median tumor volume of the treated} / \text{Median tumor volume of the control} \times 100$ . With respect to tumor growth inhibition, according to NCI standards, a  $T/C \leq 42\%$  is the minimum level of anti-tumor activity. A  $T/C < 10\%$  is considered a high anti-tumor activity level. In some embodiments, the treatment achieved by administration of a composition of the present disclosure is any of progression free survival (PFS), disease free survival (DFS) or overall survival (OS). PFS, also referred to as "Time to Tumor Progression" indicates the length of time during and after treatment that the cancer does not grow, and includes the amount of time patients have experienced a complete response or a partial response, as well as the amount of time patients have experienced stable disease. DFS refers to the length of time during and after treatment that a subject remains free of disease. OS refers to a prolongation in life expectancy as

compared to naive or untreated individuals or patients.

[00359] The term “major pathological response” (“MPR”) is defined as less than 10% residual viable tumor after neoadjuvant therapy. The 10% cutoff is determined based on the previous studies on the pathologic assessment of resected lung after neoadjuvant chemoradiotherapy (Junker K, et al. *J Cancer Res Clin Oncol*. 1997; Pataer A et al. *JTO* 2012). MPR can be observed more frequently than a pathological complete response (“pCR”), which is defined as no viable residual tumor.

[00360] While an embodiment of the compositions, treatment methods, and uses of the present disclosure may not be effective in achieving a positive therapeutic effect in every patient, it should do so in a statistically significant number of subjects as determined by any statistical test known in the art such as the Student’s t-test, the chi<sup>2</sup>-test, the U-test according to Mann and Whitney, the Kruskal-Wallis test (H-test), Cochran-Mantel-Haenszel chi-square test methodology, Jonckheere-Terpstra-test or the Wilcoxon-test.

[00361] An “immune response” refers to the action of a cell of the immune system (for example, T lymphocytes, B lymphocytes, natural killer (NK) cells, macrophages, eosinophils, mast cells, dendritic cells and neutrophils) and soluble macromolecules produced by any of these cells or the liver (including Abs, cytokines, and complement) that results in selective targeting, binding to, damage to, destruction of, and/or elimination from a vertebrate’s body of invading pathogens, cells or tissues infected with pathogens, cancerous or other abnormal cells, or, in cases of autoimmunity or pathological inflammation, normal human cells or tissues.

[00362] The terms “immunospecifically binds,” “immunospecifically recognizes,” “specifically binds,” and “specifically recognizes” are analogous terms in the context of antibodies and refer to molecules that bind to an antigen (*e.g.*, epitope or immune complex) as such binding is understood by one skilled in the art. For example, a molecule that specifically binds to an antigen may bind to other peptides or polypeptides, generally with lower affinity as determined by, *e.g.*, immunoassays, BIACORE®, KinExA 3000 instrument (Sapidyne Instruments, Boise, Id.), or other assays known in the art. Thus, under certain designated immunoassay conditions, the antibodies or antigen-binding fragments thereof specifically bind to a particular antigen at least two (2) fold when compared to the background level and do not

specifically bind in a significant amount to other antigens present in the sample. In another aspect, under designated immunoassay conditions, the antibodies or antigen-binding fragments thereof, specifically bind to a particular antigen at least ten (10) fold when compared to the background level of binding and do not specifically bind in a significant amount to other antigens present in the sample.

**[00363]** An antibody that “specifically binds to” a specified target protein is an antibody that exhibits preferential binding to that target as compared to other proteins, but this specificity does not require absolute binding specificity. An antibody is considered “specific” for its intended target if its binding is determinative of the presence of the target protein in a sample, *e.g.* without producing undesired results such as false positives. Antibodies or binding fragments thereof, useful in the present invention will bind to the target protein with an affinity that is at least two fold greater, at least ten times greater, at least 20-times greater, or at least 100-times greater than the affinity with non-target proteins. An antibody herein is said to bind specifically to a polypeptide comprising a given amino acid sequence, *e.g.* the amino acid sequence of a mature human PD-1 molecule, if it binds to polypeptides comprising that sequence but does not bind to proteins lacking that sequence.

**[00364]** The term “immunotherapy” refers to the treatment of a subject afflicted with, or at risk of contracting or suffering a recurrence of, a disease by a method comprising inducing, enhancing, suppressing or otherwise modifying an immune response. Examples of immunotherapy include, but are not limited to, T and NK cell therapies. T and NK cell therapies can include adoptive cell therapies, tumor-infiltrating lymphocyte (TIL) immunotherapies, autologous cell therapies, engineered autologous cell therapy (eACT™), and allogeneic T and NK cell transplantation.

**[00365]** The terms “improve,” “increase,” “inhibit,” and “reduce” indicate values that are relative to a baseline or other reference measurement. In some embodiments, an appropriate reference measurement may comprise a measurement in certain system (*e.g.*, in a single individual) under otherwise comparable conditions absent presence of (*e.g.*, prior to and/or after) an agent or treatment, or in presence of an appropriate comparable reference agent. In some embodiments, an appropriate reference measurement may comprise a measurement in

comparable system known or expected to respond in a comparable way, in presence of the relevant agent or treatment.

**[00366]** The term “isolated” refers to a substance that (1) has been separated from at least some components with which it was associated at an earlier time or with which the substance would otherwise be associated, and/or (2) is present in a composition that comprises a limited or defined amount or concentration of one or more known or unknown contaminants. An isolated substance, in some embodiments, may be separated from about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% (*e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%) of other non-substance components with which the substance was associated at an earlier time, *e.g.*, other components or contaminants with which the substance was previously or otherwise would be associated. In certain instances, a substance is isolated if it is present in a composition that comprises a limited or reduced amount or concentration of molecules of a same or similar type. For instance, in certain instances, a nucleic acid, DNA, or RNA substance is isolated if it is present in a composition that comprises a limited or reduced amount or concentration of non-substance nucleic acid, DNA, or RNA molecules. For instance, in certain instances, a polypeptide substance is isolated if it is present in a composition that comprises a limited or reduced amount or concentration of non-substance polypeptide molecules. In certain embodiments, an amount may be, *e.g.*, an amount measured relative to the amount of a desired substance present in a composition. In certain embodiments, a limited amount may be an amount that is no more than 100% of the amount of substance in a composition, *e.g.*, no more than 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95% of the amount of substance in a composition (*e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%). In certain instances, a composition is pure or substantially pure with respect to a selected substance. In some embodiments, an isolated substance is about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure (*e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%).

**[00367]** “Isotype” refers to the antibody class or subclass (*e.g.*, IgM or IgG1) that is encoded

by the heavy chain constant region genes. Thus, the term “antibody” includes, by way of example, both naturally occurring and non-naturally occurring antibodies; monoclonal and polyclonal antibodies; chimeric and humanized antibodies; human or nonhuman antibodies; wholly synthetic antibodies; and single chain antibodies. A nonhuman Ab may be humanized by recombinant methods to reduce its immunogenicity in man. Where not expressly stated, and unless the context indicates otherwise, the term “antibody” also includes an antigen binding fragment or an antigen-binding portion of any of the aforementioned immunoglobulins, and includes a monovalent and a divalent fragment or portion, and a single chain Ab.

**[00368]** The term “Kabat numbering” and like terms are recognized in the art and refer to a system of numbering amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen-binding molecule thereof. In certain aspects, the CDRs of an antibody can be determined according to the Kabat numbering system (*see, e.g.*, Kabat E.A. & Wu T.T. (1971) *Ann NY Acad Sci* 190: 382-391 and Kabat E.A. et al., (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). Using the Kabat numbering system, CDRs within an antibody heavy chain molecule are typically present at amino acid positions 31 to 35, which optionally can include one or two additional amino acids, following 35 (referred to in the Kabat numbering scheme as 35A and 35B) (CDR1), amino acid positions 50 to 65 (CDR2), and amino acid positions 95 to 102 (CDR3). Using the Kabat numbering system, CDRs within an antibody light chain molecule are typically present at amino acid positions 24 to 34 (CDR1), amino acid positions 50 to 56 (CDR2), and amino acid positions 89 to 97 (CDR3). In a specific embodiment, the CDRs of the antibodies described herein have been determined according to the Kabat numbering scheme.

**[00369]** The term “light chain” when used in reference to an antibody can refer to any distinct type, *e.g.*, kappa ( $\kappa$ ) or lambda ( $\lambda$ ) based on the amino acid sequence of the constant domains. Light chain amino acid sequences are well known in the art. In specific embodiments, the light chain is a human light chain.

**[00370]** The term “monoclonal antibody” or “mAb” or “Mab” herein means a population of substantially homogeneous antibodies, *i.e.*, the antibody molecules comprised in the population

are identical in amino acid sequence except for possible naturally occurring mutations that can be present in minor amounts. In contrast, conventional (polyclonal) antibody preparations typically include a multitude of different antibodies comprising different amino acid sequences in their variable domains, particularly their complementarity determining regions (CDRs), which are often specific for different epitopes. The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies and is not to be construed as requiring production of the antibody by any particular method. Monoclonal antibodies (mAbs) can be obtained by methods known to those skilled in the art (see, *e.g.*, Kohler et al., *Nature* 1975 256:495-497; U.S. Pat. No. 4,376,110; Ausubel et al., *Current Protocols in Molecular Biology* 1992; Harlow et al., *Antibodies: A Laboratory Manual*, Cold spring Harbor Laboratory 1988; and Colligan et al., *Current Protocols in Immunology* 1993).

[00371] “PD-L1 expression positive” refers to a Tumor Proportion Score, Mononuclear Inflammatory Density Score or Combined Positive Score of at least 1%; or elevated level of PD-L1 expression (protein and/or mRNA) by malignant cells and/or by infiltrating immune cells within a tumor compared to an appropriate control. In some embodiments, the elevated level of PD-L1 expression is at least 1%, 2%, 5%, 10%, 20%, or 50%.

[00372] The term “pharmaceutical composition” refers to preparations with pharmaceutically acceptable excipients which are in such form as to permit the active ingredients to be effective, and which contains no additional components which are toxic to the subjects to which the composition would be administered. In some embodiments, a pharmaceutical composition may be formulated for administration in solid or liquid form, comprising, without limitation, a form adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, *e.g.*, those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal



surfaces. In some aspects, the present disclosure provides compositions, *e.g.*, pharmaceutically acceptable compositions, which include an anti-PD-1 antibody described herein, formulated together with at least one pharmaceutically acceptable excipient. In some aspects, the present disclosure provides compositions, *e.g.*, pharmaceutically acceptable compositions, which include a chemotherapeutic drug described herein, formulated together with at least one pharmaceutically acceptable excipient.

**[00373]** The term “pharmaceutically acceptable” refers to a molecule or composition that, when administered to a recipient, is not deleterious to the recipient thereof, or that any deleterious effect is outweighed by a benefit to the recipient thereof.

**[00374]** Some examples of materials which may serve as pharmaceutically acceptable carriers comprise: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer’s solution; ethyl alcohol; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in pharmaceutical formulations.

**[00375]** A “pharmaceutically acceptable excipient” includes any and all solvents, dispersion media, isotonic and absorption delaying agents, and the like that are physiologically compatible. The excipient can be suitable for intravenous, intramuscular, subcutaneous, parenteral, rectal, spinal or epidermal administration (*e.g.*, by injection or infusion).

**[00376]** The compositions disclosed herein can be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.*, injectable and infusion solutions), dispersions or suspensions, liposomes, and suppositories. A suitable form depends on the intended mode of administration and therapeutic application. Typical suitable compositions are in the form of injectable or infusion solutions. One suitable mode of

administration is parenteral (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular). In some embodiments, the antibody is administered by intravenous infusion or injection. In certain embodiments, the antibody is administered by intramuscular or subcutaneous injection. In some embodiments, the antibody is administered by way of a syringe infusion system.

[00377] As used herein, “purifying” an antibody or antigen-binding fragment of interest or “purified composition” refers to increasing the degree of purity of the antibody or antigen binding fragment in the composition by removing (completely or partially) at least one impurity from the composition. The impurity can be host cell components such as serum, proteins or nucleic acids, cellular debris, growth medium or antibody aggregates. The term is not intended to refer to a complete absence of such biological molecules or to an absence of water, buffers, or salts or to components of a pharmaceutical composition that includes the antibody or antigen binding fragment.

[00378] “RECIST 1.1 Response Criteria” as used herein means the definitions set forth in Eisenhauer et al., *Eur. J Cancer* 45:228-247 (2009) for target lesions or nontarget lesions, as appropriate based on the context in which response is being measured.

[00379] The terms “reducing” and “decreasing” are used interchangeably herein and indicate any change that is less than the original. “Reducing” and “decreasing” are relative terms, requiring a comparison between pre- and post-measurements. “Reducing” and “decreasing” include complete depletions.

[00380] The term “reference” describes a standard or control relative to which a comparison is performed. For example, in some embodiments, an agent, animal, individual, population, sample, sequence, or value of interest is compared with a reference or control that is an agent, animal, individual, population, sample, sequence, or value. In some embodiments, a reference or control is tested, measured, and/or determined substantially simultaneously with the testing, measuring, or determination of interest. In some embodiments, a reference or control is a historical reference or control, optionally embodied in a tangible medium. Generally, a reference or control is determined or characterized under comparable conditions or circumstances to those under assessment. When sufficient similarities are present to justify reliance on and/or comparison to a selected reference or control.

[00381] “Responder patient” when referring to a specific anti-tumor response to treatment with a therapy as described herein, means the patient exhibited the anti-tumor response.

[00382] The term “stage of cancer” refers to a qualitative or quantitative assessment of the level of advancement of a cancer. In some embodiments, criteria used to determine the stage of a cancer may comprise, without limitation, one or more of where the cancer is located in a body, tumor size, whether the cancer has spread to lymph nodes, whether the cancer has spread to one or more different parts of the body, etc. In some embodiments, cancer may be staged using the so-called TNM System, according to which T refers to the size and extent of the main tumor, usually called the primary tumor; N refers to the number of nearby lymph nodes that have cancer; and M refers to whether the cancer has metastasized. In some embodiments, a cancer may be referred to as Stage 0 (abnormal cells are present without having spread to nearby tissue, also called carcinoma in situ, or CIS; CIS is not cancer, though could become cancer), Stage I-III (cancer is present; the higher the number, the larger the tumor and the more it has spread into nearby tissues), or Stage IV (the cancer has spread to visceral organs and/or distant parts of the body). In some embodiments, a cancer may be assigned to a stage selected from the group consisting of: in situ; localized (cancer is limited to the place where it started, with no sign that it has spread); regional (cancer has spread to nearby lymph nodes, tissues, or organs); distant (cancer has spread to distant parts of the body); and unknown (there is not enough information to determine the stage).

[00383] The term “subject” in the context of the present disclosure is a mammal, *e.g.*, a primate, preferably a higher primate, *e.g.*, a human (*e.g.*, a patient having, or at risk of having, a disorder described herein).

[00384] In general, two sequences are generally considered to be “substantially similar” if they contain a conservative amino acid substitution in corresponding positions. For example, certain amino acids are generally classified as “hydrophobic” or “hydrophilic” amino acids, and/or as having “polar” or “non-polar” side chains. Substitution of one amino acid for another of the same type may be considered a conservative substitution.

[00385] In general, an “effective amount” refers to an amount effective to treat a disease or disorder in a subject, and that will elicit, to some significant extent, the biological or medical

response of a tissue, system, animal or human that is being sought, such as when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being treated. The therapeutically effective amount will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated. More specifically, a “therapeutically effective amount,” “effective dose,” “effective amount,” or “therapeutically effective dosage” of a therapeutic agent, *e.g.*, an antibody, is any amount that, when used alone or in combination with another therapeutic agent, protects a subject against the onset of a disease or promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. The ability of a therapeutic agent to promote disease regression can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays. The “therapeutically effective amount” can vary with the antibody, the disease, disorder, and/or symptoms of the disease or disorder, severity of the disease, disorder, and/or symptoms of the disease or disorder, the age of the subject to be treated, and/or the weight of the subject to be treated. An appropriate amount in any given instance can be apparent to those skilled in the art or can be determined by routine experiments. In the case of combination therapy, the “therapeutically effective amount” refers to the total amount of the combination objects for the effective treatment of a disease, a disorder or a condition.

**[00386]** The terms “treatment regimen”, “dosing protocol” and “dosing regimen” are used interchangeably to refer to the dose and timing of administration of each therapeutic agent in a combination of the invention.

**[00387]** “Tumor” as it applies to a subject diagnosed with, or suspected of having, cancer refers to a malignant or potentially malignant neoplasm or tissue mass of any size, and includes primary tumors and secondary neoplasms. A solid tumor is an abnormal growth or mass of tissue that usually does not contain cysts or liquid areas. Different types of solid tumors are named for the type of cells that form them. Examples of solid tumors are sarcomas, carcinomas, and 30 lymphomas.

[00388] “Tumor burden” also referred to as “tumor load”, refers to the total amount of tumor material distributed throughout the body. Tumor burden refers to the total number of cancer cells or the total size of tumor(s), throughout the body, including lymph nodes and bone marrow. Tumor burden can be determined by a variety of methods known in the art, such as, *e.g.*, by measuring the dimensions of tumor(s) upon removal from the subject, *e.g.*, using calipers, or while in the body using imaging techniques, *e.g.*, ultrasound, bone scan, computed tomography (CT) or magnetic resonance imaging (MRI) scans.

[00389] The term “tumor size” refers to the total size of the tumor which can be measured as the length and width of a tumor. Tumor size may be determined by a variety of methods known in the art, such as, *e.g.* by measuring the dimensions of tumor(s) upon removal from the subject, *e.g.*, using calipers, or while in the body using imaging techniques, *e.g.*, bone scan, ultrasound, CT or MRI scans.

[00390] “Unidimensional irRC” refers to the set of criteria described in Nishino et al., Developing a Common Language for Tumor Response to Immunotherapy: Immune-related Response Criteria using Unidimensional measurements. Clin Cancer Res. 2013;19(14):3936-3943. These criteria utilize the longest diameter (cm) of each lesion. The term “tumor size” refers to the total size of the tumor which can be measured as the length and width of a tumor. Tumor size may be determined by a variety of methods known in the art, such as, *e.g.* by measuring the dimensions of tumor(s) upon removal from the subject, *e.g.*, using calipers, or while in the body using imaging techniques, *e.g.*, bone scan, ultrasound, CT or MRI scans.

[00391] “Tumor Proportion Score (TPS)” refers to the percentage of tumor cells expressing PD-L1 or another tumor antigen, on the cell membrane at any intensity (weak, moderate or strong). Linear partial or complete cell membrane staining is interpreted as positive for PD-L1 or another antigen of interest.

[00392] The term “variable region” or “variable domain” as used herein means the segment of IgG chains which is variable in sequence between different antibodies. Typically, it extends to Kabat residue 109 in the light chain and 113 in the heavy chain. The variability in sequence is concentrated in those regions called complementarity determining regions (CDRs) while the more highly conserved regions in the variable domain are called framework regions (FR).

Without wishing to be bound by any particular mechanism or theory, it is believed that the CDRs of the light and heavy chains are primarily responsible for the interaction and specificity of the antibody with antigen. In certain embodiments, the variable region is a human variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and human framework regions (FRs). In particular embodiments, the variable region is a primate (*e.g.*, non-human primate) variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and primate (*e.g.*, non-human primate) framework regions (FRs).

**[00393]** The terms “VH”, “VI”, “LCVR” and “VI domain” are used interchangeably to refer to the light chain variable region of an antibody.

**[00394]** The terms “VH”, “Vh”, “HCVR” and “Vh domain” are used interchangeably to refer to the heavy chain variable region of an antibody.

**[00395]** The variable regions of each light/heavy chain (VI/Vh) pair form the antibody binding site. Thus, in general, an intact antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are, in general, the same.

**[00396]** In certain embodiments, a HCVR sequence having at least 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO:24 contains substitutions (*e.g.*, conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-PD-1 antibody or antigen-binding fragment thereof comprising that sequence retains the ability to specifically bind to PD-1. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:24. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:24. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the CDRs (*i.e.*, in the FRs).

**[00397]** In certain embodiments, a LCVR sequence having at least 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO:26 contains substitutions (*e.g.*, conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-

PD-1 antibody or antigen-binding fragment thereof comprising that sequence retains the ability to specifically bind to PD-1. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:26. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:26. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the CDRs (*i.e.*, in the FRs).

[00398] Various embodiments are described hereinafter. It should be noted that the specific embodiments are not intended as an exhaustive description or as a limitation to the broader aspects discussed herein. One aspect described in conjunction with a particular embodiment is not necessarily limited to that embodiment and can be practiced with any other embodiment(s).

[00399] The present invention, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

## EXAMPLES

### **Example 1. Clinical Trial in Human Patients with Resectable Stage Non-Small Cell Lung Cancer**

*Pathological Response to Neoadjuvant Tislelizumab Plus Platinum-Doublet (PtDb)  
Chemotherapy in Resectable Stage II-III A NSCLC Patients*

[00400] This Example describes a randomized, double-blind, placebo-controlled, multicenter, Phase 3 study that was conducted, comparing the efficacy of tislelizumab (*i.e.*, an anti-PD-1 antibody) + platinum doublet (*e.g.*, cisplatin or carboplatin + etoposide) (Arm A) and placebo + platinum doublet (Arm B) as first-line treatment in 453 patients with treatment-naïve, resectable, confirmed squamous or non-squamous stage II-IIA NSCLC.

#### ***Study Objectives***

##### ***Primary Objective***

[00401] To evaluate and compare the rate of major pathological response (MPR) as assessed by Blinded Independent Pathology Review (BIPR) in patients receiving tislelizumab plus

platinum-based doublet chemotherapy versus patients receiving placebo plus platinum-based doublet chemotherapy as neoadjuvant treatment, where the MPR rate by BIPR was defined as the proportion of patients with  $\leq 10\%$  residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy as assessed by BIPR. The 10% cutoff was determined based on the previous studies on the pathologic assessment of resected lung after neoadjuvant chemoradiotherapy (Junker K, et al. *J Cancer Res Clin Oncol*. 1997; Pataer A et al. *JTO* 2012).

[00402] MPR was assessed at the time of surgery, and has been proposed by several groups as a surrogate marker for recurrence and survival in patients with solid tumor types, such colon cancer (Adam, R., 2014. *Annals of Surgical Oncology*, 21, pp.1763-1764), breast cancer (Conforti, F. et al., 2021 *Bmj*, 375), and NSCLC after neoadjuvant (perioperative) treatment.

[00403] Another primary objective was to evaluate and compare event-free-survival (EFS) as assessed by Blinded Independent Central Review (BICR) in patients receiving tislelizumab plus platinum based doublet chemotherapy as neoadjuvant treatment followed by tislelizumab as adjuvant treatment versus patients receiving placebo plus platinum based doublet chemotherapy as neoadjuvant treatment followed by placebo as adjuvant treatment, where EFS by BICR is defined as the time from randomization until any of the following events, whichever occurs first: disease progression precluding surgery, local or distant recurrence assessed by BICR, or death due to any cause.

#### *Secondary Objectives*

[00404] MPR can be observed more frequently than a pathological complete response (pCR), defined as no viable residual tumor. A secondary objective was to evaluate and compare the BIPR-assessed pCR rate of neoadjuvant treatment with tislelizumab versus placebo plus platinum-based doublet chemotherapy, where the pCR rate was defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy as assessed by BIPR.

[00405] Another secondary objective was to evaluate and compare overall survival (OS) of neoadjuvant treatment with tislelizumab plus platinum-based doublet chemotherapy followed by



adjuvant tislelizumab versus neoadjuvant treatment with placebo plus platinum-based doublet chemotherapy followed by placebo, where OS is defined as the time from the date of randomization to the date of death due to any cause. 2-year/3-year OS rate is defined as the proportion of patients alive at 2 years and 3 years after randomization estimated using the Kaplan-Meier method. The initial results support continuing this treatment combination for these patients.

#### *Other Objectives*

[00406] Correlations between programmed death ligand-1 (PD-L1) expression and clinical efficacy were also evaluated.

[00407] The association between tissue and blood-based biomarkers and clinical efficacy with Tislelizumab, functional and resistance mechanisms, and patient prognosis, were also evaluated, such as Other exploratory tissue-based biomarkers (including gene expression profiling [GEP], tumor mutation burden [TMB]/microsatellite instability(MSI)/mutation profile, multiplex immunohistochemistry [mIHC] in archival and/or fresh tumor tissue) before neoadjuvant treatment, at surgery and/or at disease progression/end of treatment (EOT) and blood-based biomarkers (including T-cell receptor [TCR] sequencing, peripheral blood immunophenotyping, and circulating tumor DNA [ctDNA]) before and after treatment to explore the predictive value for clinical efficacy, functional and resistance mechanisms of tislelizumab, and patient prognosis.

#### *Brief Description of Methods*

[00408] The study enrolled 453 patients with treatment-naïve, resectable, confirmed squamous or non-squamous stage II-IIA NSCLC who were eligible for platinum doublet chemotherapy, with ECOG PS < 1 and no known EGFR mutations (nsq) or ALK gene translocations (sq & nsq). Patients stratified by histology, disease stage, and PD-L1 expression were randomized (1:1) to 3-4 cycles of Tislelizumab 200 mg IV (Q3W) or placebo plus platinum double chemotherapy, followed by surgery plus 8 cycles of adjuvant Tislelizumab 400 mg IV Q6W or placebo. The primary endpoint was major pathological response rate (MPR) after completion of neoadjuvant treatment plus event-free survival (EFS) as determined by RECIST v1.1 by blinded independent review (BIRC). The key secondary endpoints were pCR and safety.

Tumor lesions were measured by CT scan or X-ray before treatment and then after 200 mg.

*Summary of Study Design*

[00409] Test Product (Investigational Drug) (Arm A): (1) Tislelizumab: 200 mg, Day 1 of each 3-week cycle, administered as an intravenous (IV) infusion for 3 to 4 cycles during the neoadjuvant phase. (2) Tislelizumab: 400 mg, Day 1 of each 6-week cycle, administered as an IV infusion for up to 8 cycles during the adjuvant phase.

[00410] Comparator (Arm B): (1) Placebo: Day 1 of each 3-week cycle, administered as an IV infusion for 3 to 4 cycles during the neoadjuvant phase. (2) Placebo: Day 1 of each 6-week cycle, administered as an IV infusion for up to 8 cycles during the adjuvant phase.

[00411] The study consisted of a Screening phase, a Treatment phase that included a Neoadjuvant phase, Surgery and an Adjuvant phase. A Safety follow-up phase, and a Survival follow-up phase concluded the study.

*Screening Phase*

[00412] Key Inclusion Criteria:

- Age  $\geq$  18 years on the day of signing the informed consent form (or the legal age of consent in the jurisdiction in which the study is taking place).
- ECOG Performance Status of 0 or 1.  
Histologically confirmed Stage II or IIIA NSCLC (per the Eighth American Joint Committee on Cancer/Union International Contre le Cancer NSCLC staging system).
- Measurable disease as assessed by the investigator per RECIST v1.1.
- Evaluation by an attending thoracic surgeon to confirm eligibility for an R0 resection with curative intent.
- Adequate cardiopulmonary function to be eligible for surgical resection with curative intent.
- Eligibility to receive a platinum-based doublet chemotherapy regimen.
- Adequate hematologic and end organ function, defined by protocol -specified laboratory test results, obtained within 14 days before randomization.

**[00413]** Key Exclusion Criteria:

- Any prior therapy for current lung cancer, including chemotherapy, or radiotherapy.
- Patients with large cell neuroendocrine carcinoma (LCNEC).
- Known EGFR mutation or ALK gene translocation.
- Patients with non-squamous NSCLC and unknown EGFR mutation status were required to be tested locally or at a central laboratory before enrollment.
- Patients with squamous NSCLC and unknown EGFR mutation status were not required to be tested at screening.
- Patients (non-squamous or squamous histology) with unknown ALK fusion oncogene status were not required to be tested.
- Presence of locally advanced unresectable regardless of stage or metastatic disease (Stage IV). Mediastinal lymph node samples are required for clinical staging to assess nodal involvement in patients with mediastinal adenopathy on CT scan to rule out Stage IIIB/C disease.
- Any condition requiring systemic treatment with either corticosteroids ( $> 10$  mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days before randomization.
- Adrenal replacement steroid (dose  $\leq 10$  mg daily of prednisone or equivalent) and topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption, and short course ( $\leq 7$  days) of corticosteroid prescribed prophylactically or for the treatment of a non-autoimmune condition were permitted.

*Neoadjuvant Phase*

**[00414]** Eligible patients were stratified by disease stage (II versus IIIA), histology (squamous versus non squamous) and PD-L1 expression ( $\geq 1\%$  versus  $< 1\%$ /not evaluable/indeterminate), and randomized in a 1:1 ratio to 1 of the following treatment arms:

- Arm A: tislelizumab (200 mg) + platinum-based doublet chemotherapy on a 3-week cycle for 3 to 4 cycles, followed by surgical resection, and then adjuvant tislelizumab (400 mg) on a 6-week cycle for up to 8 cycles

- Arm B: placebo + platinum-based doublet chemotherapy on a 3-week cycle for 3 to 4 cycles, followed by surgical resection, and then placebo on a 6-week cycle for up to 8 cycles

The following platinum-based doublet chemotherapy options were permitted for this study:

- Cisplatin/Carboplatin + Pemetrexed (non-squamous).
- Cisplatin/Carboplatin + Paclitaxel (squamous).

[00415] Carboplatin could replace cisplatin per the investigator's discretion in consideration of patient's tolerability to cisplatin. The reasons for intolerability were documented. During the neoadjuvant phase, patients who were found to have disease progression (at scheduled tumor assessments or at any time during neoadjuvant treatment) or who discontinued neoadjuvant treatment early with tumor(s) still deemed to be resectable and nonmetastatic proceeded to surgery if amenable.

#### *Surgery*

[00416] Upon completion of neoadjuvant therapy, patients underwent surgical resection of their tumor. Surgical specimens were assessed for pathological response (MPR and pCR) by a BIPR. In addition, exploratory biomarker analysis of surgical specimens (primary tumor tissue and dissected lymph nodes) were performed.

[00417] Before surgery, the investigator assessed the patient to reconfirm disease resectability. The presurgical visit and associated assessments occurred within 14 days of surgery and in accordance with local institutional practice.

[00418] The surgical procedure was performed between 4 and 6 weeks after the last dose of neoadjuvant study treatment. Before the surgery, patients underwent tumor assessment by CT every 6 weeks ( $\pm$  1 week) since last tumor assessment with ethical considerations.

#### *Adjuvant Phase*

[00419] The following criteria must be met to treat patients in the adjuvant phase:

- Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1

- Recovered from surgery with adequate organ function as indicated by the laboratory values confirmed by the investigator

[00420] During the adjuvant phase, patients received tislelizumab (400 mg) (Arm A) or placebo (Arm B) as adjuvant treatment. For patients who did not undergo postoperative radiotherapy (PORT), the first dose of tislelizumab/placebo (Cycle 1 in the adjuvant phase) was administered between 2 and 8 weeks after surgery; initial dosing beyond 8 weeks was discussed with the medical monitor. PORT was optional for patients with pathologically confirmed N2+ disease after surgery at the investigator's discretion. PORT began between 30 and 60 days after surgery and was in accordance with the American Society for Radiation Oncology recommended guidelines or local guidelines. Adjuvant treatment was administered between 7 and 30 days after the last scheduled PORT treatment and patients when recovered from any radiation-associated toxicities.

[00421] Patients continued to receive adjuvant tislelizumab (400 mg) (Arm A) or placebo (Arm B) on a 6-week cycle until any of the following occurred: administration of 8 cycles of tislelizumab/placebo as adjuvant treatment, disease recurrence, unacceptable AE, death, or patient and/or investigator's decision to discontinue study treatment.

#### *Disease Measurement*

[00422] Patients underwent scheduled tumor assessment scans of the chest and abdomen by computed tomography (CT) (CT contrast media, unless contraindicated), scans of the brain by contrast enhanced magnetic resonance imaging (MRI), and scans of the whole body by positron emission tomography (PET) at screening. Patients underwent scheduled tumor assessment scans of the chest and abdomen by CT within 14 days before Cycle 3 of neoadjuvant treatment and before surgery. Chest CT + abdomen CT + pelvis CT + bone scan were an alternative option for sites that could not provide PET scan for various reasons. Before surgery, the investigator reassessed the patient to reconfirm disease resectability. The presurgical visits and associated assessments occurred within 14 days of surgery and in accordance with local institutional practice. After surgery, disease follow-up and tumor assessment were performed by chest and upper abdomen CT.

[00423] All patients were assessed for safety and tolerability on Day 1 of each cycle in the neoadjuvant and adjuvant phases. Patients returned to the clinic for a Safety Follow-up Visit not more than 30 days ( $\pm 7$  days) after the last dose of study treatment.

[00424] Response and progression were evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (v1.1) (Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-47). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions were used in the RECIST criteria.

[00425] Tumor lesions were measured in at least 1 dimension (longest diameter in the plane of measurement recorded) with a minimum size of:

- 10 mm by CT and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (when superficial).
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

#### *Primary Efficacy Analysis*

[00426] MPR as assessed by the BIPR and EFS as assessed by the BICR:

[00427] MPR rate assessed by the BIPR was defined as the proportion of patients with  $\leq 10\%$  residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy as assessed by BIPR. Patients who did not receive surgical resection were considered as non-responders in the analysis.

[00428] EFS assessed by the BICR was defined as the time from randomization until any of the following events, whichever occurs first: disease progression precluding surgery, local or distant recurrence assessed by BICR, or death due to any cause. A disease progression not reaching the RECIST v1.1 criteria by BICR but still precluding surgery (progressive disease or tumor un-resectability assessed by investigator) was still considered an event. Patients who did not undergo surgery due to reasons other than progressive disease and tumor un-resectability

were considered to have had an event of RECIST v1.1 defined progression by BICR or death.

**[00429]** An actual tumor assessment visit date was used to calculate EFS. Patients who died without a progression/disease recurrence were considered to have experienced an event on the date of their death. MPR per BIPR was compared between tislelizumab combined with platinum-based doublet chemotherapy (Arm A) and placebo combined with platinum-based doublet chemotherapy (Arm B), using Cochran-Mantel-Haenszel chi-square test methodology. EFS per BICR was compared between Arm A and Arm B, using stratified log-rank test methodology.

#### *Biomarkers*

**[00430]** Archival tumor tissues (formalin-fixed paraffin-embedded [FFPE] block or approximately 15 [ $\geq$  6] unstained slides) were sent for immunohistochemistry assay (IHC) of PD-L1 status. In addition to PD-L1 expression, other predictive biomarkers, such as TMB and immune-mediated GEP (gene expression profiles), biomarkers expression by multiplex IHC, and other immune-mediated markers that are related to response or clinical benefit of tislelizumab were evaluated. If no archival samples were available, a fresh tumor biopsy at screening was taken, if feasible. For fresh biopsy specimens, acceptable samples included core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

**[00431]** Blood samples were taken at baseline (pre-dose at Day 1 of Cycle 1) and optionally at the time of disease progression and/or at the time of first tumor response (CR/PR) (10 mL each timepoint) for all randomized patients to explore the association of blood-based biomarkers with response, resistance, and prognosis to tislelizumab in combination with chemotherapy or chemotherapy alone.

**[00432]** Distribution of PD-L1 expression was examined in the ITT Analysis Set. Any potential association between PD-L1 expression and tislelizumab treatment effect over control (PFS, OS, ORR, DOR, and DCR) was explored. Other potential predictive markers, including but not limited to GEP, TMB and MSI (micro-satellite instability) in archival and/or fresh tumor tissue and bTMB were assessed before study treatment and/or at disease progression. The association with disease status and/or response to tislelizumab in combination with

chemotherapy was assessed.

## Results

### *Summary of Results*

**[00433]** The study enrolled patients with treatment-naïve, resectable, confirmed squamous or non-squamous stage II-IIA NSCLC who were eligible for platinum doublet chemotherapy, with ECOG PS < 1 and no known EGFR mutation (nsq) or ALK gene translocation (sq & nsq). Patients stratified by histology, disease stage, and PD-L1 expression were randomized (1:1) to 3-4 cycles of Tislelizumab 200 mg IV (Q3W) or placebo plus platinum double chemotherapy, followed by surgery plus 8 cycles of adjuvant Tislelizumab 400 mg IV Q6W or placebo. The primary endpoint was major pathological response rate after completion of neoadjuvant treatment plus event-free survival (EFS) as determined by RECIST v1.1 by blinded independent review. The key secondary endpoints were pCR and safety.

**[00434]** After a median follow-up time of 16.8 months, 453 patients (TIS+CT, n=226; CT, n=227) were randomized to the Intention-To-Treat (ITT) population and had similar baseline characteristics. Of 452 (99.8%; n=226 both arms) patients treated in the neoadjuvant phase, 421 (92.9%) completed neoadjuvant treatment (TIS + CT, n=211 [93.4%]; CT, n=210 [92.5%]); 90 (19.9%) did not undergo surgery (TIS + CT, n=36 [15.9%]; CT, n=54 [23.8%]). Efficacy data from the neoadjuvant phase are summarized in Table 9 below.

| Table 9. Efficacy data from the neoadjuvant phase   |                                    |                  |
|-----------------------------------------------------|------------------------------------|------------------|
|                                                     | TIS + CT                           | CT               |
|                                                     | Intention-To-Treat (ITT) Set       |                  |
|                                                     | n=226                              | n=227            |
| MPR, % (95% CI) <sup>a</sup>                        | 56.2 (49.5-62.8)                   | 15.0 (10.6-20.3) |
| Difference, % (95% CI); <i>P</i> value <sup>b</sup> | 41.1 (33.2-49.1); <i>P</i> < .0001 |                  |
| OR (95% CI); <i>P</i> value <sup>b</sup>            | 7.5 (4.8-11.8); <i>P</i> < .0001   |                  |
| pCR, % (95% CI)                                     | 40.7 (34.2-47.4)                   | 5.7 (3.1-9.6)    |
| Difference, % (95% CI); <i>P</i> value <sup>b</sup> | 35.0 (27.9-42.1); <i>P</i> < .0001 |                  |



| Table 9. Efficacy data from the neoadjuvant phase |                          |
|---------------------------------------------------|--------------------------|
| OR (95% CI); P value <sup>b</sup>                 | 11.5 (6.2-21.5); P<.0001 |

<sup>a</sup> Assessed by blinded independent review committee (IRC)

<sup>b</sup> 1-sided

Abbreviations: MPR, major pathological response; OR, odds ratio; pCR, pathological complete response.

**Neoadjuvant Anti-PD-1 Therapy Plus Chemotherapy Is Effective for the Treatment of Lung Cancer**

*Clinical Trial Efficacy Conclusions*

[00435] Major pathological response (MPR) and pathological complete response (pCR) rates were significantly improved with Tislelizumab in combination with chemotherapy versus placebo plus chemotherapy (56.2 percent for the combination of Tislelizumab and chemotherapy prior to surgery versus 15.0 percent for placebo plus chemotherapy alone).

[00436] Overall, Tislelizumab in combination with chemotherapy prior to surgery as first-line treatment for patients with untreated NSCLC demonstrated significant clinical benefit and a manageable safety profile compared to placebo plus chemotherapy alone prior to surgery.

**Example 2: A Study to Compare the Efficacy and Safety of Neoadjuvant Treatment With Tislelizumab (BGB-A317, Anti-PD-1 Antibody) or Placebo Plus Platinum-Based Doublet Chemotherapy Followed By Adjuvant Tislelizumab or Placebo in Resectable Stage II or IIIA Non-Small Cell Lung Cancer**

[00437] This example describes a Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Compare the Efficacy and Safety of Neoadjuvant Treatment With Tislelizumab (BGB-A317, Anti-PD-1 Antibody) or Placebo Plus Platinum-Based Doublet Chemotherapy Followed By Adjuvant Tislelizumab or Placebo in Resectable Stage II or IIIA Non-Small Cell Lung Cancer.

*Primary Objectives and Endpoints:*

[00438] Objectives: (1) To evaluate and compare major pathological response (MPR) rate assessed by Blinded Independent Pathology Review (BIPR) in patients receiving tislelizumab plus platinum-based doublet chemotherapy versus patients receiving placebo plus platinum-based doublet chemotherapy as neoadjuvant treatment. (2) To evaluate and compare event free survival (EFS) assessed by Blinded Independent Central Review (BICR) in patients receiving tislelizumab plus platinum-based doublet chemotherapy as neoadjuvant treatment followed by tislelizumab as adjuvant treatment versus patients receiving placebo plus platinum based doublet chemotherapy as neoadjuvant treatment followed by placebo as adjuvant treatment.

[00439] Endpoints: (1) MPR rate by BIPR is defined as the proportion of patients with  $\leq 10\%$  residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy as assessed by BIPR. (2) EFS by BICR is defined as the time from randomization until any of the following events, whichever occurs first: disease progression precluding surgery, local or distant recurrence assessed by BICR, or death due to any cause.

#### *Secondary Objectives and Endpoints*

[00440] Objectives:

- To evaluate and compare BIPR-assessed pathological complete response (pCR) rate of neoadjuvant treatment with tislelizumab- versus placebo plus platinum-based doublet chemotherapy.

- To evaluate and compare overall survival (OS) of neoadjuvant treatment with tislelizumab plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab versus neoadjuvant treatment with placebo plus platinum-based doublet chemotherapy followed by placebo.

- To evaluate and compare objective response rate of neoadjuvant treatment with tislelizumab- versus placebo plus platinum-based doublet chemotherapy before surgery assessed by BICR and by investigator, respectively.

- To evaluate and compare BICR-assessed disease-free survival (DFS) of adjuvant tislelizumab treatment versus placebo after completely resection (R0).

- To evaluate and compare investigator assessed EFS of neoadjuvant treatment with tislelizumab plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab versus neoadjuvant treatment with placebo plus platinum-based doublet chemotherapy followed by adjuvant placebo.

- To evaluate and compare the safety and tolerability of neoadjuvant treatment with tislelizumab plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab versus neoadjuvant treatment with placebo plus platinum-based doublet chemotherapy followed by placebo by treatment-emergent adverse events (TEAEs).

- To evaluate and compare health-related quality of life (HRQoL) of neoadjuvant treatment with tislelizumab plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab versus neoadjuvant treatment with placebo plus platinum-based doublet chemotherapy followed by placebo.

**[00441]** Endpoints:

- The pCR rate is defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy as assessed by BIPR.

- OS is defined as the time from the date of randomization to the date of death due to any cause. 2-year/3-year OS rate is defined as the proportion of patients alive at 2 years and 3 years after randomization estimated using the Kaplan-Meier method.

- Objective response rate is the proportion of patients who had complete response (CR) or partial response (PR) as assessed by BICR and by the investigator per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) in all randomized patients with measurable disease at baseline.

- DFS by BICR is defined as the time from the first date of no disease to local or distant recurrence or death due to any cause, whichever occurs first, as determined by BICR during the adjuvant treatment and safety follow-up.

- EFS by investigator is defined as the time from randomization until any of the following events, whichever occurs first: disease progression precluding surgery, local or distant recurrence

assessed by investigator, or death due to any cause. 2-year/3-year EFS rate is defined as the proportion of patients free from EFS events at 2 years and 3 years after randomization estimated using the Kaplan-Meier method.

- Incidence and severity of TEAEs, including serious adverse events (SAEs) and immune mediated adverse events (imAEs), with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0).

- HRQoL—measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer (EORTC QLQ-LC13), Core 30 (EORTC QLQ C30), and European Quality of Life 5 Dimensions (EQ-5D-5L), defined as changes in most relevant lung cancer symptoms (dyspnea, dysphagia, coughing, chest pain, pain in the arm and shoulders, hemoptysis, peripheral neuropathy, and fatigue), global health status (GHS), and physical function.

#### ***Other Study Objectives and Endpoints***

##### **[00442] Objectives:**

- Assess the outcome of surgery, including feasibility and rate of peri- and postoperative complications.
- To characterize pharmacokinetics (PK) of tislelizumab in patients with resectable Stage II or IIIA non-small cell lung cancer (NSCLC).
- To evaluate host immunogenicity to tislelizumab by assessing antidrug antibodies (ADAs) against tislelizumab.
- To evaluate correlations of programmed death ligand-1 (PD-L1) expression and clinical efficacy.
- To evaluate the association of potential tissue and blood-based biomarkers of tislelizumab with clinical efficacy, functional and resistance mechanisms, and patient prognosis.

##### **[00443] Endpoints:**

- Feasibility assessments include surgery (delayed or canceled), duration of surgery, length of hospital stay, surgical type and approach, resection status, and incidence of AEs/SAEs associated with surgery.

- Summary of serum concentrations of tislelizumab.

- Assessments of immunogenicity of tislelizumab by determining the incidence of ADAs.

- PD-L1 expression as the predictive biomarker for efficacy (including but not limited to MPR and EFS).

- Other exploratory tissue based biomarkers (including gene expression profiling [GEP], tumor mutation burden [TMB]/microsatellite instability(MSI)/mutation profile, multiplex immunohistochemistry [mIHC] in archival and/or fresh tumor tissue) before neoadjuvant treatment, at surgery and/or at disease progression/end of treatment (EOT) and blood based biomarkers (including T-cell receptor [TCR] sequencing, peripheral blood immunophenotyping, and circulating tumor DNA [ctDNA]) before and after treatment to explore the predictive value for clinical efficacy, functional and resistance mechanisms of tislelizumab, and patient prognosis.

### ***Study Design***

[00444] The study is designed as a randomized, double-blind, placebo-controlled Phase 3 study to compare the efficacy and safety of neoadjuvant treatment with tislelizumab plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab treatment versus neoadjuvant treatment with placebo plus platinum-based doublet chemotherapy followed by placebo in patients with resectable Stage II or IIIA NSCLC.

[00445] The study consists of a screening phase, a treatment phase that includes a neoadjuvant phase, surgery and an adjuvant phase, a safety follow-up phase, and a survival follow-up phase. The study schema is presented in **FIG. 1**.

### ***Treatment Period***

#### ***Neoadjuvant Phase***

[00446] Eligible patients are stratified by disease stage (II versus IIIA), histology (squamous versus non squamous) and PD-L1 expression ( $\geq 1\%$  versus  $< 1\%$ /not evaluable/indeterminate),

and randomized in a 1:1 ratio to 1 of the following treatment arms:

**Arm A:** tislelizumab (200 mg) + platinum-based doublet chemotherapy on a 3-week cycle for 3 to 4 cycles, followed by surgical resection, and then adjuvant tislelizumab (400 mg) on a 6 week cycle for up to 8 cycles

**Arm B:** placebo + platinum-based doublet chemotherapy on a 3-week cycle for 3 to 4 cycles, followed by surgical resection, and then placebo on a 6-week cycle for up to 8 cycles.

There are the following platinum-based doublet chemotherapy options:

Cisplatin/Carboplatin + Pemetrexed (non-squamous)

Cisplatin/Carboplatin + Paclitaxel (squamous)

[00447] Carboplatin can replace cisplatin per physician's discretion in consideration of patient's tolerability to cisplatin. For patients with tumors of mixed histology (squamous and non-squamous), appropriate chemotherapy regimen is decided by physicians based on the major histological components assessed by pathologists.

#### *Surgery*

[00448] Upon completion of neoadjuvant therapy, patients undergo surgical resection of their tumor. Surgical specimens are assessed for pathological response (MPR and pCR) by a BIPR. In addition, exploratory biomarker analysis of surgical specimens (primary tumor tissue and dissected lymph nodes) is performed.

[00449] Before surgery, physician reassesses the patient to reconfirm disease resectability. The presurgical visit and associated assessments should occur within 14 days of surgery and in accordance with local institutional practice.

[00450] The surgical procedure should be performed between 4 and 6 weeks after the last dose of neoadjuvant study treatment as best as possible. Before the surgery, patients undergo tumor assessment by CT every 6 weeks ( $\pm 1$  week) since last tumor assessment with ethical considerations.

#### *Adjuvant Phase*

**[00451]** The following criteria must be met to treat patients in the adjuvant phase:

- Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1
- Recovered from surgery with adequate organ function as indicated by the laboratory values confirmed by the investigator

**[00452]** During the adjuvant phase, patients receive tislelizumab (400 mg) (Arm A) or placebo (Arm B) as adjuvant treatment. For patients who do not undergo postoperative radiotherapy (PORT), the first dose of tislelizumab/placebo (Cycle 1 in the adjuvant phase) should be administered between 2 and 8 weeks after surgery; initial dosing beyond 8 weeks should be discussed with the medical monitor. PORT is optional for patients with pathologically confirmed N2+ disease after surgery at the investigator's discretion. Either PORT or another surgical procedure is administered for patients with positive surgical margins before starting adjuvant treatment per standard of care. PORT should begin between 30 and 60 days after surgery and be in accordance with the American Society for Radiation Oncology recommended guidelines or local guidelines. Adjuvant treatment should be administered between 7 and 30 days after the last scheduled PORT treatment and patients should have recovered from any radiation-associated toxicities.

**[00453]** Patients continue to receive adjuvant tislelizumab (400 mg) (Arm A) or placebo (Arm B) on a 6-week cycle until any of the following occurs: administration of 8 cycles of tislelizumab/placebo as adjuvant treatment, disease recurrence, unacceptable AE, death, or patient and/or investigator's decision to discontinue study treatment.

Crossover between the 2 study arms is not allowed.

**[00454]** Patients undergo scheduled tumor assessment scans of the chest and abdomen by computed tomography (CT) (CT contrast media, unless contraindicated), scans of the brain by contrast enhanced magnetic resonance imaging (MRI), and scans of the whole body by positron emission tomography (PET) at screening. Patients undergo scheduled tumor assessment scans of the chest and abdomen by CT within 14 days before Cycle 3 of neoadjuvant treatment and before surgery. Chest CT + abdomen CT + pelvis CT + bone scan should be an alternative option for

sites that could not provide PET scan for various reasons. Before surgery, physician reassesses the patient to reconfirm disease resectability. The presurgical visit and associated assessments should occur within 14 days of surgery and in accordance with local institutional practice. After surgery, disease follow-up tumor assessment is performed by chest and upper abdomen CT every 12 weeks after surgery for the first 2 years, every 24 weeks for Years 3 to 5, and then annually thereafter based on RECIST v1.1. Tumor assessments must continue per protocol until disease recurrence/progression confirmed by BICR per RECIST v1.1, withdrawal of consent, death, loss to follow-up, or study termination by the sponsor, whichever occurs first.

[00455] Safety is assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per NCI-CTCAE v5.0) and laboratory results. Vital signs, physical examinations, ECOG Performance Status change, electrocardiogram (ECG) results, and other examinations are also used for safety assessment.

#### **Dosage and Administration**

[00456] Dosing schedules for the 2 study arms are provided in FIG. 1 by arm. The first dose of study drug(s) is to be administered within 2 business days of randomization. All patients are monitored continuously for AEs. Treatment modifications (*e.g.* dose delay, reduction, or interruption), or discontinuation will be based on specific laboratory and AE criteria.

[00457] During the neoadjuvant phase, for each cycle, tislelizumab or placebo are administered before chemotherapy drugs. The order of chemotherapy drug administration is conducted in accordance with the relevant local guidance and/or clinical practice.

[00458] Patients should receive antiemetics and intravenous hydration for chemotherapy according to the standard of care and manufacturer's instruction. Due to their immunomodulatory effects, premedication with steroids should be limited when clinically feasible. In addition, in the event of chemotherapeutic agent-related skin rash, topical steroid use is recommended as treatment whenever it is clinically feasible.

[00459] In special situations (*e.g.* when the administration is delayed due to management of AEs or in the case of an infusion-related reaction), administration of the subsequent study drugs might be delayed to the second day of each cycle.



| <b>Table 10: Selection and Timing of Dose for Each Patient</b> |                       |                                    |                                |                                                               |
|----------------------------------------------------------------|-----------------------|------------------------------------|--------------------------------|---------------------------------------------------------------|
| <b>Study Drug</b>                                              | <b>Dose</b>           | <b>Frequency of Administration</b> | <b>Route of Administration</b> | <b>Duration of Treatment</b>                                  |
| Tislelizumab                                                   | 200 mg                | Day 1 of every 3 weeks             | IV                             | 3 to 4 cycles during the neoadjuvant phase                    |
| Placebo                                                        | NA                    | Day 1 of every 3 weeks             | IV                             |                                                               |
| Tislelizumab                                                   | 400 mg                | Day 1 of every 6 weeks             | IV                             | Up to 8 cycles during the adjuvant phase                      |
| Placebo                                                        | NA                    | Day 1 of every 6 weeks             | IV                             |                                                               |
| Cisplatin                                                      | 75 mg/m <sup>2</sup>  | Day 1 of every 3 weeks             | IV                             | 3 to 4 cycles during the neoadjuvant phase                    |
| Carboplatin                                                    | AUC of 5 mg/mL/min    | Day 1 of every 3 weeks             | IV                             |                                                               |
| Pemetrexed                                                     | 500 mg/m <sup>2</sup> | Day 1 of every 3 weeks             | IV                             | 3 to 4 cycles during the neoadjuvant phase (for non-squamous) |
| Paclitaxel                                                     | 175 mg/m <sup>2</sup> | Days 1 of every 3 weeks            | IV                             | 3 to 4 cycles during the neoadjuvant phase (for squamous)     |

Abbreviation: AUC, area under the curve; IV, intravenous(ly); NA, not applicable.

#### *Tislelizumab or Placebo*

**[00460]** Tislelizumab 200 mg (or placebo) is administered on Day 1 of each 21-day cycle (once every 3 weeks) in the neoadjuvant phase, while in the adjuvant phase, tislelizumab 400 mg (or placebo) is administered on Day 1 of each 42-day cycle (once every 6 weeks).

**[00461]** Tislelizumab or placebo is administered by intravenous infusion through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

**[00462]** The initial infusion (Cycle 1, Day 1) in the neoadjuvant phase is delivered over 60 minutes; if this is well tolerated, then the subsequent infusions may be administered over 30 minutes, which is the shortest time period permissible for infusion. The initial infusion (Cycle 1, Day 1) in the adjuvant phase is delivered over 90 minutes; if this is well tolerated, the second infusion may be administered over 60 minutes; and for each subsequent infusion, over 30

minutes if 60 minutes infusion is tolerated. Tislelizumab or placebo must not be concurrently administered with any other drug.

#### *Chemotherapy*

[00463] Patients receive treatment with platinum-based doublet chemotherapy during the neoadjuvant phase (Table 10).

[00464] Cisplatin 75 mg/m<sup>2</sup> is administered as an intravenous infusion over 2 hours on Day 1 of each 3-week cycle for 3 to 4 cycles. All patients should receive adequate hydration (including pretreatment hydration) and diuretics. Urinary output must be maintained for at least 24 hours following cisplatin administration. Monitoring is performed according to local guidance and clinical practice.

[00465] Carboplatin AUC of 5 mg/mL/min is administered as an intravenous infusion over 1 hour on Day 1 of each 3-week cycle for 3 to 4 cycles. Carboplatin can replace cisplatin per the investigator's discretion in consideration of patient's tolerability to cisplatin. The reasons for intolerability should be documented.

[00466] For non-squamous: Pemetrexed 500 mg/m<sup>2</sup> is administered as an intravenous infusion over 10 minutes on Day 1 of each 3-week cycle for 3 to 4 cycles. All patients should receive the appropriate supplementation of vitamin B12 and folic acid according to the approved product label and/or standard practice. In addition, all patients should receive the appropriate corticosteroid premedications as per the local approved label. Additional premedications should be administered as per standard practice.

[00467] For squamous: Paclitaxel 175 mg/m<sup>2</sup> is administered as an intravenous infusion over 3 hours on Day 1 of each 3-week cycle for 3 to 4 cycles. In addition, all patients should receive the appropriate premedications as per the local approved labels. Additional premedications should be administered as per standard practice.

[00468] The length of infusion period for cisplatin, carboplatin, pemetrexed, and paclitaxel could also follow the approved label or local practice. The administered dose could be adjusted within  $\pm 5\%$  of the calculated dose at the investigator's discretion.

[00469] Patients are monitored continuously for AEs and are instructed to notify their

physician immediately for any and all AEs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of each therapy.

*Dose Delay or Modification OF Tislelizumab of Placebo*

[00470] There is no dose reduction for tislelizumab or placebo in this study.

[00471] Patients may temporarily suspend study treatment if they experience toxicity that is considered related to tislelizumab and requires a dose to be withheld. The patients should resume tislelizumab or placebo treatment as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) and within 12 weeks after last dose of tislelizumab or placebo. If the patient is unable to resume tislelizumab or placebo within 12 weeks after the last dose of tislelizumab or placebo, then the patient should be discontinued from treatment.

[00472] If a patient is benefiting from the study treatment while meeting the discontinuation criteria, resumption of study treatment may occur.

*Dose Delay, Interruption, or Modifications for Chemotherapy*

[00473] Treatment modifications for chemotherapy should be performed per prescribing information and per local practice according to the investigator's clinical judgment.

[00474] Baseline body weight is used to calculate the required chemotherapy doses. Treatment modifications are required if the patient's body weight changes by  $\geq 10\%$  from baseline (or the new reference body weight). Chemotherapy doses should not be modified for any body weight change of  $< 10\%$ .

[00475] Study drug-related toxicities must be resolved to baseline level, or Grade 0 or 1 before administering the next dose (except for alopecia or Grade 2 fatigue). A maximum of 2 dose reductions for each chemotherapeutic agent except for carboplatin are permitted. Only 1 dose reduction is permitted for carboplatin. Once the dose has been decreased, it should remain reduced for all subsequent administrations or further reduced if necessary. There are no dose escalations in this study. If additional reductions are required, that chemotherapeutic agent must be discontinued.

[00476] When a treatment cycle is delayed or interrupted because of toxicity resulting from

either component of the chemotherapy regimen, all study drugs (including tislelizumab or placebo) should generally be withheld and resumed together to remain synchronized. At the subsequent cycle, if chemotherapy still cannot be given due to prolonged AE and toxicities, then tislelizumab or placebo should be given for that cycle alone. If chemotherapy has been withheld for 42 days (delayed cycle + subsequent cycle), then it should permanently be discontinued.

### STUDY POPULATION

[00477] The study population includes approximately 450 patients who have histologically confirmed Stage II or IIIA NSCLC.

#### *Patient Inclusion Criteria Include:*

[00478] Each patient eligible to participate in this study must meet all the following criteria:

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments.
2. Age  $\geq 18$  years on the day of signing the ICF (or the legal age of consent in the jurisdiction in which the study is taking place).
3. Histologically confirmed Stage II or IIIA NSCLC of squamous or non-squamous histology:
  - Staging should be based on the eighth edition of the American Joint Committee on Cancer/Union International Contre le Cancer NSCLC staging system.
  - T4 primary NSCLC will be allowed only on the basis of size (tumors  $> 7$  cm). Invasion of the diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, and separate tumor nodules in a different ipsilateral lobe is not permitted.
  - Patients with mixed NSCLC histology (squamous and non-squamous) or NSCLC not otherwise specified are eligible.
  - Patients may be enrolled based on clinical stage, but pre-operative documentation of nodal involvement by endobronchial ultrasound or mediastinoscopy is strongly encouraged.
4. Archival tumor tissues (FFPE blocks or approximately 15  $\geq 6$  freshly cut unstained FFPE slides) with an associated pathological report at baseline are required to be provided for

PD-L1 and other biomarker analysis (an additional  $\geq 6$  slides are required if EGFR central laboratory testing applicable). If archival samples are unavailable or deemed to be unsuitable, a fresh biopsy at baseline is required.

5. Solid or subsolid appearance of NSCLC on CT scan with no appearance of purely ground glass opacity.

- For subsolid lesions, the tumor size (ie, clinical T stage) should be measured based on solid component only, exclusive of the ground-glass opacity component.

6. Evaluation by an attending thoracic surgeon to confirm eligibility for an R0 resection with curative intent.

7. Pulmonary function tests within 6 months of planned resection and repeated at screening, if clinically indicated, including lung volumes, spirometry, and a diffusion capacity.

- Abnormal pulmonary function tests may be further evaluated with quantitative ventilation/perfusion scanning or cardiopulmonary exercise testing.

- Postoperative percent predicted forced expiratory volume in 1 second (FEV1) and diffusion capacity must be  $\geq 40\%$  and/or maximal oxygen consumption (VO<sub>2</sub>max) should be  $> 10$  mL/kg/min.

8. Adequate cardiopulmonary function to be eligible for surgical resection with curative intent.

- If clinically indicated, patients with underlying ischemic, valvular, or other significant heart diseases should be evaluated preoperatively by a cardiologist.

9. Measurable disease as assessed by the investigator per RECIST v1.1.

10. Eligibility to receive a platinum-based doublet chemotherapy regimen.

- For patients intended to receive cisplatin: without any hearing impairment.

11. ECOG Performance Status 0 or 1.

12. Adequate organ function as indicated by the following laboratory values obtained  $\leq 14$  days before randomization.

- Patients must not have required blood transfusion or growth factor support  $\leq 14$  days before sample collection at screening for the following:

- Absolute neutrophil count  $\geq 1.5 \times 10^9/L$

- Platelets  $\geq 100 \times 10^9/L$
- Hemoglobin  $\geq 90 \text{ g/L}$
- Calculated creatinine clearance (CrCl) (Cockcroft-Gault formula)
- For patients intended to receive cisplatin: creatinine clearance  $\geq 60 \text{ mL/min}$
- For patients intended to receive carboplatin: creatinine clearance  $\geq 45 \text{ mL/min}$
- Serum total bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN) (total bilirubin must be  $< 3 \times$  ULN for patients with Gilberts syndrome).
- AST and ALT  $\leq 2.5 \times$  ULN
- For patients not receiving therapeutic anticoagulation: international normalized ratio or activated partial thromboplastin time  $\leq 1.5 \times$  ULN.

**[00479]** Patient Exclusion Criteria Include:

**[00480]** Patients who meet any of the following criteria are not eligible to enroll:

1. Any prior therapy for current lung cancer, including chemotherapy, or radiotherapy.
2. Prior treatment with an antibody or drug against immune checkpoint pathway, including but not limited to, anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4), anti PD-1, and anti-PD-L1 therapeutic antibodies.
3. Patients with large cell neuroendocrine carcinoma (LCNEC).
4. Known EGFR mutation or ALK gene translocation.
  - For non-squamous patients, a documentation of wild type EGFR reported by a tissue based test is required. For non-squamous patients without documented EGFR status, EGFR mutation testing locally or at a central laboratory before enrollment is mandatory.
  - Patients with squamous NSCLC and unknown EGFR mutation status will not be required to be tested at screening.
  - Patients (non-squamous or squamous histology) with unknown ALK fusion oncogene status will not be required to be tested.
5. Presence of locally advanced unresectable regardless of stage or metastatic disease (Stage IV). Mediastinal lymph node samples are required for clinical staging to assess nodal

involvement in patients with mediastinal adenopathy on CT scan to rule out Stage IIIB/C disease.

6. Active autoimmune diseases or history of autoimmune diseases that may relapse.

Note: Patients with the following diseases are not excluded and may proceed to further screening:

- Controlled Type I diabetes
- Hypothyroidism (provided it is managed with hormone replacement therapy only)
- Controlled celiac disease
- Skin diseases not requiring systemic treatment (*e.g.*, vitiligo, psoriasis, alopecia)
- Any other disease that is not expected to recur in the absence of external

triggering factors

7. Any active malignancy  $\leq 2$  years before randomization except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (*e.g.*, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast).

8. Any condition that required systemic treatment with either corticosteroids ( $> 10$  mg daily of prednisone or equivalent) or other immunosuppressive medication  $\leq 14$  days before randomization.

Note: Patients who are currently or have previously been on any of the following steroid regimens are not excluded:

- Adrenal replacement steroid (dose  $\leq 10$  mg daily of prednisone or equivalent)
- Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal

systemic absorption

- Short course ( $\leq 7$  days) of corticosteroid prescribed prophylactically (*e.g.*, for contrast dye allergy) or for the treatment of a non-autoimmune condition (*e.g.*, delayed-type hypersensitivity reaction caused by contact allergen)

9. With uncontrolled diabetes or  $>$  Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or  $\geq$  Grade 3 hypoalbuminemia  $\leq 14$  days before randomization

10. With history of interstitial lung disease, non-infectious pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc.
11. Severe chronic or active infections requiring systemic antibacterial, antifungal or antiviral therapy, including tuberculosis infection, etc.
  - Severe infections within 4 weeks before randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.
  - Received therapeutic oral or intravenous antibiotics within 2 weeks before randomization.
12. A known history of HIV infection.
13. Patients with untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers whose HBV DNA is  $\geq 500$  IU/mL or patients with active hepatitis C virus (HCV) should be excluded.

Note: Inactive hepatitis B surface antigen carriers, treated and stable hepatitis B (HBV DNA  $< 500$  IU/mL), and cured hepatitis C patients can be enrolled.
14. Any major surgical procedure requiring general anesthesia  $\leq 28$  days before randomization.
15. Prior allogeneic stem cell transplantation or organ transplantation.

**[00481]** Patient Exclusion Criteria Include:

16. Any of the following cardio/cerebrovascular risk factors:
  - Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living,  $\leq 28$  days before randomization
  - Pulmonary embolism  $\leq 28$  days before randomization
  - Any history of acute myocardial infarction  $\leq 6$  months before randomization
  - Any history of heart failure meeting New York Heart Association Classification III or IV  $\leq 6$  months before randomization
  - Any event of ventricular arrhythmia  $\geq$  Grade 2 in severity  $\leq 6$  months before randomization
  - Any history of cerebrovascular accident  $\leq 6$  months before randomization



- Uncontrolled hypertension that cannot be managed by standard anti-hypertension medications  $\leq 28$  days before randomization
  - Any episode of syncope or seizure  $\leq 28$  days before randomization
17. A history of severe hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
18. Has received any chemotherapy, immunotherapy (*e.g.*, interleukin, interferon, thymosin) or any investigational therapies within 14 days or 5 half-lives (whichever is shorter) of the first study drug administration.
19. Patients with toxicities (as a result of prior anticancer therapy) which have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (*e.g.*, alopecia, neuropathy, and specific laboratory abnormalities).
20. Was administered a live vaccine  $\leq 4$  weeks before randomization.
- Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines and live vaccines are not allowed.
21. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that, will be unfavorable for the administration of study drug or affect the explanation of drug toxicity or AEs or result in insufficient or might impair compliance with study conduct.

### ***Prior and Concomitant Therapy***

#### ***i. Prior Therapy***

[00482] The exclusion criteria specify that patients must not have received prior therapy for current lung cancer, including chemotherapy and radiotherapy, and prior treatment with an antibody or drug against immune checkpoint pathways, including but not limited to, anti-PD-1, anti-PD-L1, or anti-CTLA-4.

[00483] All prior and concomitant medications (*e.g.*, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) received within 30 days before randomization and 30 days after the last dose of study treatment (as of Safety Follow-up Visit) should be recorded.

#### ***ii. Permitted Concomitant Medications and Procedures***

[00484] Most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the investigator for supportive care (*e.g.*, antiemetics, antidiarrheals) and in a patient's interest are allowed. Patients should receive full supportive care, including epoetin and other hematopoietic growth factors, transfusions of blood and blood products, antibiotics, antiemetics, and/or other applicable medications, as needed. Management of prophylaxis antiviral therapy for patients with inactive HBsAg, treated and stable hepatitis B (HBV DNA < 500 IU/mL) is at the discretion of the investigator, as aligned with local guidance; however, reason(s) must be documented in patient's chart and recorded in the eCRF if a patient with active hepatitis B is not treated with antiviral prophylaxis.

[00485] Systemic corticosteroids given for the control of imAEs must be tapered gradually and be at nonimmunosuppressive doses ( $\leq 10$  mg/day of prednisone or equivalent) before the next tislelizumab/placebo administration. The short-term use of steroids as prophylactic treatments (*e.g.*, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

*iii. Prohibited Concomitant Medications and Procedures*

[00486] The following medications are prohibited during the study:

- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other Country) herbal medicine] for the treatment of cancer) is not allowed.
- Live vaccines within 28 days before randomization and 60 days after the last dose of study drug(s)
- Herbal remedies with immune-stimulating properties (*e.g.*, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (*e.g.*, hypericin). Patients must notify the investigator of all herbal remedies used during the study.
- Ibuprofen administration should be avoided or restricted in patients with a creatinine clearance between 45 mL/min and 79 mL/min.
- If concomitant ibuprofen use cannot be avoided, at a minimum, administration of ibuprofen should be avoided for 2 days before the day of, and 2 days after administration of

pemetrexed, and monitor patients more frequently for adverse reactions, including myelosuppression, renal, and gastrointestinal toxicity (pemetrexed prescribing information).

*iv. Restricted Concomitant Medications and Procedures*

[00487] The following medications are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE)
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug related AE (per protocol) or for short-term use as prophylactic treatment
- Patients should not abuse alcohol or other drugs during the study.
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored.
- Radiation therapy is not allowed, except for post operative radiotherapy.

Patients must notify the investigator of all concurrent medications used during the study.

*Tumor and Response Evaluations*

[00488] Patients undergo scheduled tumor assessment scans of the chest and abdomen by computed tomography (CT) (CT contrast media, unless contraindicated), scans of the brain by contrast-enhanced magnetic resonance imaging (MRI), and scans of the whole body by positron emission tomography (PET) at screening. Patients undergo scheduled tumor assessment scans of the chest and abdomen by CT within 14 days before Cycle 3 of neoadjuvant treatment and before surgery. Chest CT + abdomen CT + pelvis CT + bone scan should be an alternative option for sites that could not provide PET scan for various reasons. Before surgery, disease resectability is reconfirmed. The presurgical visit and associated assessments should occur within 14 days of surgery and in accordance with local institutional practice. After surgery, disease follow-up tumor assessment is performed by chest and upper abdomen CT every 12 weeks after surgery for the first 2 years, every 24 weeks for Years 3 to 5, and then annually thereafter based on RECIST v1.1. Tumor assessments must continue per protocol until disease recurrence/progression confirmed by BICR per RECIST v1.1, withdrawal of consent, death, loss to follow-up, or study termination by the sponsor, whichever occurs first.

[00489] All patients are assessed for safety and tolerability on Day 1 of each cycle in the neoadjuvant and adjuvant phases. Patients will return to the clinic for a Safety Follow-up Visit not more than 30 days ( $\pm$  7 days) after the last dose of study treatment.

[00490] AEs are evaluated according to NCI-CTCAE v5.0. After initiation of study drug(s), all AEs and SAEs, regardless of relationship to study drug(s), are reported until 30 days after the last dose of study drug(s) or until the end of treatment, whichever occurs later. Immune-mediated AEs (serious or nonserious) are reported until 90 days after the last dose of tislelizumab or placebo, regardless of whether the patient starts a new anticancer therapy.

[00491] HRQoL is assessed using the EORTC QLQ-LC13, EORTC QLQ-C30, and EQ-5D-5L at baseline (predose at Day 1 of Cycle 1); at Cycle 3 during the neoadjuvant phase; at Cycles 1, 3, 5, and 7 during the adjuvant phase; and at the Safety Follow-up Visit.

[00492] The same radiographic procedure used to assess disease sites at screening are required to be used throughout the study (*e.g.*, the same contrast protocol for CT scans).

- Screening evaluations are performed within 28 days before randomization.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced magnetic resonance imaging (MRI) (if possible) of abdomen should be performed.
- If a CT scan for tumor assessment is performed on a PET/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan. This replacement should be evaluated and confirmed at site level with BICR.

[00493] For immune therapies such as tislelizumab, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to apparent increase of existing tumor masses or appearance of new tumor lesions. The following criteria must be met to treat patients with suspected pseudoprogression or confirmed evidence of disease progression:

- Absence of clinical symptoms and signs of disease progression (including clinically significantly worsening of laboratory values)

- ECOG Performance Status 0 or 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (*e.g.*, cord compression) that requires urgent alternative medical intervention

#### ***Pharmacokinetic and Anti-Drug Antibody Testing***

[00494] Validated screening and confirmatory assays are employed to detect ADAs at multiple timepoints throughout the study. The immunogenicity evaluation utilizes a risk-based immunogenicity strategy (Koren et al J Immunol Methods. 2008;333(1-2):1-9; Worobec and Rosenberg BioPharm Intl 2004a;17(11); Worobec and Rosenberg BioPharm Intl 2004b;17(12)) to characterize ADA responses to tislelizumab. This tiered strategy will include an assessment of whether ADA responses correlate with relevant clinical endpoints. The following assessments are performed at a bioanalytical laboratory:

- ADA assays: serum samples are tested for the presence of ADAs to tislelizumab using a validated immunoassay
- PK assay: serum samples are assayed for tislelizumab concentration with use of a validated immunoassay

#### ***Biomarker Testing***

[00495] For biomarker assessment, archival tumor tissues (FFPE block or approximately 15  $\geq$  6] additional unstained slides) at baseline are sent for immunohistochemistry assessment of PD-L1 status as one of the stratification factors. Other baseline tissue-based biomarkers including mIHC, immune-related GEP, and TMB/MSI/mutation profile are also assessed. Surgical tumor tissue (FFPE block or approximately 15  $\geq$  6] unstained slides) is collected and sent for biomarker analysis (including PD-L1 expression, mIHC, immune-related GEP, and TMB/MSI/mutation profile). For fresh biopsy specimens, acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

[00496] Blood samples are collected at Day 1 of Cycle 1 and Cycle 2 during both neoadjuvant and adjuvant phases (about 15 mL for each timepoint) to explore the association of blood-based

biomarkers (including TCR sequencing, peripheral blood immunophenotyping) with response, resistance, and prognosis. Blood samples are collected at predose on Day 1 of Cycle 1 and Day 1 of Cycle 3 during the neoadjuvant phase and at predose on Day 1 of Cycle 1 during the adjuvant phase (about 20 mL for each timepoint) to evaluate biomarkers including ctDNA by molecular methods. Changes in biomarkers such as ctDNA may provide evidence of biologic activity of tislelizumab combination treatment in humans. Correlations between these biomarkers and efficacy endpoints is explored to identify blood-based biomarkers that may help identify patients who are more likely to benefit from tislelizumab combination treatment.

### *Statistical Analysis*

[00497] Patients are randomized using the IRT system for this study by permuted block stratified randomization with stratification factors of histology (non-squamous versus squamous), disease stage (II versus IIIA) and PD-L1 expression ( $\geq 1\%$  versus  $< 1\%$ /not evaluable/indeterminate).

### *Analysis Sets*

- The ITT Analysis Set includes all randomized patients. Patients are analyzed according to their randomized treatment arms. This will be the primary analysis set for all efficacy analyses, including analyses of MPR, pCR, and EFS endpoints.
- The Safety Analysis Set includes all randomized patients who received  $\geq 1$  dose of any component of study drugs; it will be the analysis set for the safety analyses. Patients are analyzed according to the actual treatment regimen received.
- The PK Analysis Set includes all patients who receive  $\geq 1$  dose of tislelizumab per the protocol, for whom any postbaseline PK data are available.
- The Immunogenicity Analysis Set includes all patients who received  $\geq 1$  dose of tislelizumab and for whom both baseline ADA and  $\geq 1$  postbaseline ADA results are available.

### *Efficacy Analyses*

[00498] The ITT Analysis Set is the primary analysis set for all efficacy analyses.

*i. Primary Efficacy Analysis*

[00499] MPR rate assessed by the BIPR is defined as the proportion of patients with  $\leq 10\%$  residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy as assessed by BIPR. Patients who do not receive surgical resection are considered as nonresponders in analysis.

[00500] EFS assessed by the BICR is defined as the time from randomization until any of the following events, whichever occurs first: disease progression precluding surgery, local or distant recurrence assessed by BICR, or death due to any cause. A disease progression not reaching the RECIST v1.1 criteria by BICR but still precludes surgery (progressive disease or tumor unresectability assessed by investigator) is considered an event. Patients who do not undergo surgery due to reasons other than progressive disease and tumor unresectability are considered to have an event of RECIST v1.1 defined progression by BICR or death.

[00501] Actual tumor assessment visit date is used to calculate EFS. Patients who die without a progression/disease recurrence are considered to have experienced an event on the date of their death. Patients who did not report progression/recurrence of disease or die are censored on the date of their last evaluable tumor assessment. Patients who did not have any on-study tumor assessment and did not die are censored on the date they were randomized. Patients who started any subsequent anticancer therapy outside of the protocol-specified adjuvant therapy without a prior reported progression/recurrence are censored at the last evaluable tumor assessment before initiation of the subsequent anticancer therapy.

[00502] MPR per BIPR is compared between tislelizumab combined with platinum-based doublet chemotherapy (Arm A) and placebo combined with platinum-based doublet chemotherapy (Arm B), using Cochran-Mantel-Haenszel chi-square test methodology. EFS per BICR is compared between Arm A and Arm B, using stratified log-rank test methodology. The 2 dual primary hypothesis tests are formed as follows:

**One-sided testing of MPR superiority of Arm A to Arm B:**

[00503] The null hypothesis to be tested is:

$H_0$ : MPR in Arm A  $\leq$  MPR in Arm B

Against the alternative hypothesis:

$H_a$ : MPR in Arm A  $>$  MPR in Arm B

MPR rate per the BIPR is computed in each arm with the exact 95% CI using Clopper-Pearson method. The odds ratio between Arm A and Arm B stratified by histology, disease stage, and PD-L1 expression is provided along with the 95% CI using Mantel-Haenszel method. In addition, an estimate of the difference in MPR and corresponding 95% CI is calculated using Cochran-Mantel-Haenszel methodology and adjusted by stratification factors.

**One-sided testing of EFS superiority of Arm A to Arm B:**

[00504] The null hypothesis to be tested is:

$H_0$ : EFS in Arm A  $\leq$  EFS in Arm B

Against the alternative hypothesis:

$H_a$ : EFS in Arm A  $>$  EFS in Arm B

The p-values from a stratified log-rank test is presented using stratification factors in the IRT at randomization. The HR for EFS for Arm A versus Arm B is estimated using a stratified Cox regression model. The 95% CI for the HR will be provided. Unstratified analysis will also be presented. Kaplan-Meier methodology is used to estimate median EFS for each treatment arm, and a Kaplan-Meier curve is constructed to provide a visual description of the difference among arms.

**Subgroup Analysis for MPR and EFS**

[00505] Subgroup analysis of primary endpoint of MPR and EFS is conducted to determine whether the treatment effect is consistent across various subgroups. On the basis of information available at the time of developing this analysis plan, attention is given to the following factors:

- Histology (non-squamous versus squamous)
- Disease stage (II versus IIIA)
- PD-L1 expression in TC ( $\geq 1\%$  versus  $< 1\%$ /not evaluable/indeterminate)



- Smoking status (smoker versus non-smoker)
- Age ( $\leq 65$  versus  $> 65$  years)
- Gender (female versus male)
- ECOG Performance Status (0 versus 1)
- Surgical margins (positive versus negative)

*ii. Secondary Efficacy Analysis*

Key secondary analysis

*pCR as assessed by BIPR*

[00506] The pCR rate by BIPR is defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy. Patients who do not receive surgical resection is considered as nonresponders in analysis. After success of MPR testing, pCR per BIPR is compared between tislelizumab combined with platinum-based doublet chemotherapy (Arm A) and placebo combined with platinum-based doublet chemotherapy (Arm B), using Cochran-Mantel-Haenszel chi-square test methodology. Similar methodology used to evaluate MPR per the BIPR is applied to analyze pCR per BIPR.

Other secondary analyses

*Overall Survival*

[00507] OS is defined as the time from the date of randomization to the date of death due to any cause. Data for patients who are not reported as having died at the time of analysis is censored at the date last known to be alive. Data for patients who do not have postbaseline information is censored at the date of randomization. OS distribution is estimated using Kaplan-Meier method. Comparison of OS between Arm A versus Arm B is tested at the earliest data cutoff when MPR, pCR, and EFS tests are statistically significant using the stratified log-rank test.

*2-year/3-year OS rate*

[00508] 2-year/3year OS rate is defined as the proportion of patients alive at 2 years and 3 years after randomization estimated using Kaplan-Meier method. The difference in OS rate and corresponding 95% CI is calculated using Cochran-Mantel-Haenszel methodology and adjusted by stratification factors for descriptive purpose.

*Event-Free Survival by investigator*

[00509] EFS by the investigator is defined as the time from randomization until any of the following events, whichever occurs first: disease progression precluding surgery, local or distant recurrence assessed by investigator, or death due to any cause. The same analysis method and censoring rule of EFS by BICR is applied to analysis of EFS by investigator except that log-rank test for EFS by investigator is for descriptive purposes only.

*2-year/3-year EFS rate*

[00510] 2-year/3-year EFS rate is defined as the proportion of patients free from EFS events at 2 years and 3 years after randomization estimated using Kaplan-Meier method. Similar methodology used to evaluate OS rate is applied to EFS rate analysis.

*Objective response rate per BICR and per the investigator*

[00511] Objective response rate (confirmation not required according to RECIST v1.1) is the proportion of patients who had CR or PR as assessed by BICR and by the investigator per RECIST v1.1 in all randomized patients with measurable disease at baseline. Patients without any postbaseline assessment are considered nonresponders. Similar methodology used to evaluate MPR per the BIPR is applied to objective response rate analysis.

*DFS per the BICR*

[00512] DFS by BICR is defined as the time from the first date of no disease to local or distant recurrence or death due to any cause, whichever occurs first, as determined by BICR during the adjuvant treatment and safety follow-up. DFS is analyzed only for patients who underwent R0 resection. If patients were alive without recurrence, DFS was determined from the first date of no disease to the date of last known date and is censored on the date of last known date. DFS is estimated using Kaplan-Meier methodology.

*iii. Other Efficacy Analyses*

[00513] Any potential association between PD-L1 expression and tislelizumab treatment effect over control (MPR, EFS, pCR, objective response rate, and DFS) is explored. Other biomarkers including GEP, TMB/MSI/mutant profile, mIHC in archival and/or fresh tumor tissue and TCR sequencing, peripheral blood immunophenotyping, and ctDNA in blood is assessed before, during, or after study treatment or at disease progression/reoccurrence, and the association with efficacy, mechanism, and patient prognosis is assessed.

**RESPONSE CRITERIA***Evaluation of Target Lesions*

[00514] Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

[00515] Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

[00516] Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (Note: the appearance of one or more new lesions is also considered progression).

[00517] Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

*Duration of Overall Response*

[00518] The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

[00519] The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

*Duration of Stable Disease*

- Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

**Example 3: Tislelizumab and Chemotherapy/Chemoradiotherapy as Neoadjuvant Treatment for Resectable Esophageal Squamous Cell Carcinoma**

[00520] For patients with locally advanced resectable esophageal squamous cell carcinoma (R-ESCC), perioperative chemoradiotherapy (CRT) followed by esophagectomy is the current standard of care. However, implementation of preoperative CRT is not satisfactory for various reasons, including, for example, greater safety concerns than with neoadjuvant chemotherapy alone.

[00521] This example describes an ongoing Phase 2, Multicenter, Open-Label, 2-cohort Study to investigate the efficacy and safety of positron emission tomography (PET) guided neoadjuvant treatment with Tislelizumab (BGB-A317) plus chemotherapy/chemoradiotherapy in patients R-ESCC. The purpose of this study was to evaluate the pathological complete response (pCR) in participants receiving tislelizumab plus chemotherapy/chemoradiotherapy as neoadjuvant treatment. Primary analysis results are presented herein.

*Summary of Study Design*

[00522] Patients with R-ESCC and no prior therapy were enrolled and, after a baseline PET/CT scan, received one cycle of induction paclitaxel plus cisplatin chemotherapy followed by a second PET/CT scan. Patients were categorized into “responder” or “non-responder” cohorts and allocated to tislelizumab plus chemotherapy or tislelizumab plus CRT, respectively, followed by surgery (**FIG. 3**).

[00523] Experimental Cohort A (Responder): Participants with a decrease in positron emission tomography (PET) Standardized Uptake Value (SUV)  $\max \geq 35\%$  received 3 cycles of tislelizumab (200 mg/cycle) plus 2 cycles of chemotherapy double (cisplatin + paclitaxel). Tislelizumab was administered intravenously as specified in the treatment arm.

[00524] Experimental Cohort B (Non-responder): Participants with a decrease in PET SUVmax < 35% received 3 cycles of tislelizumab (200 mg/cycle) plus 2 cycles of investigator-chosen chemotherapy doublet (paclitaxel + cisplatin or 5-fluorouracil + cisplatin) plus concurrent radiotherapy (40 grays/20 fractions). Tislelizumab was administered intravenously as specified in the treatment arm.

#### *Study Objectives*

[00525] The primary and secondary outcome measures are summarized below. Major pathological response (MPR) rate was assessed as an exploratory endpoint.

[00526] Primary Outcome Measures: Pathological complete response (pCR) Rate: The pCR was defined as the proportion of participants with absence of residual tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant treatment. pCR will be monitored for approximately 5 years.

#### Secondary Outcome Measures:

[00527] R0 Resection Rate: Defined as the proportion of participants with R0 resection. R0 resection rate will be monitored for approximately 5 years.

[00528] 1-year/3-year Disease-free Survival (DFS) Rate: The DFS was defined as the proportion of participants free from disease events at 1st year and 3rd year after the first date of no disease. The DFS was defined as the time from the first date of no disease (R0 resection as surgery outcome) to local or distant recurrence or death due to any cause, whichever occurs first. The DFS rate will be analyzed only for participants who undergo R0 resection. The DFS rate will be monitored for approximately 5 years.

[00529] 1-year/3-year Event-free Survival (EFS) Rate: The EFS was defined as the proportion of participants free from EFS events at 1st year and 3rd year after the first dose. The EFS was defined as the time from the time of first dose until any of the following events, whichever occurs first: progression of disease that precludes definitive surgery, local or distant recurrence, or death due to any cause. The EFS rate will be monitored for approximately 5 years.

[00530] Objective Response Rate (ORR): The ORR was defined as the proportion of participants who have a complete response or partial response before surgery as assessed by the

investigator per RECIST v1.1 in all participants with measurable disease at baseline. The ORR will be monitored for approximately 5 years.

[00531] Number Of Participants Experiencing Treatment-Emergent Adverse Events will be monitored for approximately 5 years.

*Screening Phase*

Key Inclusion Criteria:

[00532] Eastern Cooperative Oncology Group Performance Status of 0 or 1.

[00533] Histologically confirmed esophageal squamous cell carcinoma (ESCC).

[00534] Stage cT1-2N+M0 and cT3NanyM0 (per The American Joint Committee on Cancer 8th Edition).

[00535] Evaluation by the investigator to confirm eligibility for an R0 resection with curative intent.

[00536] Adequate hematologic and organ function, defined by protocol-specified laboratory test results obtained within 14 days before first dose.

Key Exclusion Criteria:

[00537] Ineligible for treatment with any of the chemotherapy doublets of protocol-specified chemotherapy.

[00538] Any prior therapy for current ESCC, including investigational agents, chemotherapy, radiotherapy, targeted therapy agents, or prior therapy with an anti-programmed cell death protein-1, anti-programmed cell death protein ligand-1, anti-programmed cell death protein ligand-2, or any other antibody or drug specifically targeting T-Cell co-stimulation or checkpoint pathways.

[00539] History of fistula due to primary tumor invasion.

[00540] Participants with high risk of fistula or sign of perforation evaluated by investigator.

[00541] Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days before first

dose.

[00542] \* Adrenal replacement steroid (dose  $\leq$  10 mg daily of prednisone or equivalent) and topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption, and short course ( $\leq$  7 days) of corticosteroid prescribed prophylactically or for the treatment of a non-autoimmune condition are permitted.

[00543] Active autoimmune diseases or history of autoimmune diseases that may relapse.

[00544] \* Controlled Type I diabetes, hypothyroidism only requiring hormone replacement, controlled celiac disease, skin diseases (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

[00545] History of interstitial lung disease, non-infectious pneumonitis or uncontrolled diseases including pulmonary fibrosis, acute lung diseases.

[00546] With infections requiring systemic antibacterial, antifungal, or antiviral therapy, including tuberculosis infection

- Severe infections within 4 weeks before first dose, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.
- Receive therapeutic oral or intravenous antibiotics within 2 weeks before first dose.

### *Results*

[00547] As a neoadjuvant treatment guided by positron emission tomography/computed tomography (PET/CT) response after chemotherapy induction in patients with resectable esophageal squamous cell carcinoma (R-ESCC), tislelizumab plus chemotherapy/chemoradiotherapy demonstrated promising pathological complete response (pCR) rates in both PET/CT-assessed responders (chemotherapy cohort) and non-responders (chemoradiotherapy cohort), with tolerable safety.

### Baseline Characteristics and Treatment Exposure

[00548] 70 patients were enrolled in the study, the majority of which (68.6%) had stage III

disease at initial diagnosis (**Table 11**). All patients received induction chemotherapy. 30 patients were PET/CT-assessed responders and 40 patients were assessed as non-responders (**Table 11**). Among the 30 responders, 39 received three cycles of tislelizumab and 27 received two cycles of paclitaxel and cisplatin. Among the 40 non-responders, 34 received three cycles of tislelizumab and two cycles of paclitaxel and cisplatin, with 34 receiving 40 Gy radiotherapy. At data cutoff, the median study follow-up time was 9.7 months (range 3.6-19.9).

| <b>Table 11: Patient Baseline Characteristics (Safety Analysis Set)</b> |                          |                              |                     |
|-------------------------------------------------------------------------|--------------------------|------------------------------|---------------------|
|                                                                         | <b>Responders (n=30)</b> | <b>Non-responders (n=40)</b> | <b>Total (n=70)</b> |
| Age                                                                     |                          |                              |                     |
| Median, years (range)                                                   | 67.5 (47-75)             | 63.5 (51-79)                 | 64.0 (47-79)        |
| Age ≥65 years, n (%)                                                    | 18 (60.0)                | 16 (40.0)                    | 34 (48.6)           |
| Male, n (%)                                                             | 24 (80.0)                | 38 (95.0)                    | 62 (88.6)           |
| ECOG PS, n (%)                                                          |                          |                              |                     |
| 0                                                                       | 15 (50.0)                | 17 (42.5)                    | 32 (45.7)           |
| 1                                                                       | 15 (50.0)                | 23 (57.5)                    | 38 (54.3)           |
| Disease stage at initial diagnosis, n (%)                               |                          |                              |                     |
| II                                                                      | 7 (23.3)                 | 8 (20.0)                     | 15 (21.4)           |
| III                                                                     | 18 (60.0)                | 30 (75.0)                    | 48 (68.6)           |
| IVA                                                                     | 5 (16.7)                 | 2 (5.0)                      | 7 (10.0)            |
| Primary location of esophageal cancer, n (%)                            |                          |                              |                     |
| Upper thoracic                                                          | 3 (10.0)                 | 8 (20.0)                     | 11 (15.7)           |
| Middle thoracic                                                         | 16 (53.3)                | 16 (40.0)                    | 32 (45.7)           |
| Lower thoracic                                                          | 10 (33.3)                | 15 (37.5)                    | 25 (35.7)           |
| Esophagogastric junction                                                | 1 (3.3)                  | 1 (2.5)                      | 2 (2.9)             |

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status

### Efficacy

[00549] Among the 30 responders, 21 underwent surgery, with a pCR rate of 28.6% (n=6/21; 95% CI: 11.3, 52.2) and a R0 resection rate of 95.2% (n=20/21) (**Table 12**). Among the 40 non-



responders, 33 underwent surgery, with a pCR rate of 33.3% (n=11/33; 95% CI: 18.0, 51.8) and a R0 resection rate of 90.9% (n=30/33) (**Table 12**). Percentage of residual viable tumor in responders and non-responders is presented in **FIG. 4A-4B**.

| <b>Table 12: Efficacy Summary</b>                                                      |                          |                              |
|----------------------------------------------------------------------------------------|--------------------------|------------------------------|
| <b>Efficacy Evaluable Analysis Set<sup>a</sup></b>                                     |                          |                              |
|                                                                                        | <b>Responders (n=21)</b> | <b>Non-responders (n=33)</b> |
| <b>pCR, n (%); [95% CI]<sup>b</sup></b>                                                | 6 (28.6); [11.3, 52.2]   | 11 (33.3); [18.0, 51.8]      |
| <b>MPR<sup>c</sup>, n (%); [95% CI]<sup>b</sup></b>                                    | 10 (47.6); [25.7, 70.2]  | 19 (57.6); [39.2, 74.5]      |
| <b>Percentage of residual viable tumor, n (%)</b>                                      |                          |                              |
| 0                                                                                      | 6 (28.6)                 | 11 (33.3)                    |
| 0 to ≤10                                                                               | 4 (19.0)                 | 8 (24.2)                     |
| 10 to ≤25                                                                              | 1 (4.8)                  | 1 (3.0)                      |
| 25 to ≤50                                                                              | 3 (14.3)                 | 3 (9.1)                      |
| >50                                                                                    | 3 (14.3)                 | 8 (24.2)                     |
| <b>R0 resection, n (%)</b>                                                             | 20 (95.2)                | 30 (90.9)                    |
| <b>Patients With Measurable Disease at Baseline in Safety Analysis Set<sup>d</sup></b> |                          |                              |
|                                                                                        | <b>Responders (n=21)</b> | <b>Non-responders (n=33)</b> |
| <b>ORR<sup>e</sup>, n (%); [95% CI]<sup>b</sup></b>                                    | 15 (71.4); [47.8, 88.7]  | 14 (42.4); [25.5, 60.8]      |
| <b>Best overall response, n (%)</b>                                                    |                          |                              |
| Complete response                                                                      | 1 (4.8)                  | 3 (9.1)                      |
| Partial response                                                                       | 14 (66.7)                | 11 (33.3)                    |

| Table 12: Efficacy Summary |          |           |
|----------------------------|----------|-----------|
| Stable disease             | 5 (23.8) | 15 (45.5) |
| Progressive disease        | 1 (4.8)  | 1 (3.0)   |
| Could not be determined    | 0 (0.0)  | 3 (9.1)   |

Data cutoff: 17 April 2023. <sup>a</sup>Efficacy evaluable analysis set includes all patients who received neoadjuvant treatment followed by surgery; <sup>b</sup>95% CI was estimated using the Clopper-Pearson method; <sup>c</sup>Defined as the proportion of patients with ≤10% residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy; <sup>d</sup>Safety analysis set includes all enrolled patients who receive one or more dose of any component of study drugs; <sup>e</sup>ORR before surgery. **Abbreviations:** CI, confidence interval; MPR, major pathological response; ORR, objective response rate; pCR, pathological complete response.

Safety

[00550] Treatment-related treatment emergent adverse events (TRAEs) of grade ≥3 were reported in 46.7% and 82.5% of patients in responders and non-responders, respectively (**Table 13**). TRAEs of grade ≥3 reported in ≥10% patients included neutrophil count decreased (36.7%) among responders, and neutrophil count decreased (65.0%), white blood cell count decreased (47.5%), lymphocyte count decreased (17.5%), and anemia (12.5%) among non-responders. The majority of grade ≥3 TRAEs were related to chemotherapy or radiotherapy components of treatment. Tislelizumab-related treatment emergent adverse events (TEAEs) of grade ≥3 were reported in 10.0% and 22.5% of patients in the responder and non-responder cohorts, respectively.

[00551] No TRAEs leading to death were reported, few patients experienced TEAEs leading to treatment discontinuation or surgery delay, and no patients had surgery cancelled due to a TEAE

[00552] All immune-mediated adverse events were grade 1 or 2. Surgery relevant adverse

events were reported in 76.2% and 63.6% of responders and non-responders, respectively.

| <b>Table 13: Safety Summary (Safety Analysis Set)</b> |                           |                              |
|-------------------------------------------------------|---------------------------|------------------------------|
| <b>Patients, n (%)</b>                                | <b>Responders (n=30)</b>  | <b>Non-responders (n=40)</b> |
| <b>TEAE of any grade</b>                              | 30 (100.0)                | 40 (100.0)                   |
| Treatment-related <sup>a</sup>                        | 28 (93.3)                 | 40 (100.0)                   |
| <b>TEAE of grade <math>\geq 3</math></b>              | 24 (80.0)                 | 34 (85.0)                    |
| Treatment-related <sup>a</sup>                        | 14 (46.7)                 | 33 (82.5)                    |
| <b>Serious TEAE</b>                                   | 8 (26.7)                  | 12 (30.0)                    |
| Treatment-related <sup>a</sup>                        | 5 (16.7)                  | 8 (20.0)                     |
| <b>TEAE leading to death</b>                          | 1 (3.3)                   | 1 (2.5)                      |
| Treatment-related <sup>a</sup>                        | 0 (0.0)                   | 0 (0.0)                      |
| <b>TEAE leading to any treatment discontinuation</b>  | 1 (3.3)                   | 4 (10.0)                     |
| <b>TEAE leading to surgery cancellation</b>           | 0 (0.0)                   | 0 (0.0)                      |
| <b>TEAE leading to surgery delay</b>                  | 1 (3.3)                   | 5 (12.5)                     |
| <b>Immune-mediated adverse events</b>                 | 5 (16.7)                  | 5 (12.5)                     |
| <b>Surgery relevant adverse events<sup>b</sup></b>    | 16/21 (76.2) <sup>c</sup> | 21/33 (63.6) <sup>c</sup>    |

Data cutoff: 17 April 2023. <sup>a</sup>Any study treatment component related TEAEs, including tislelizumab, chemotherapy, or radiotherapy; <sup>b</sup>Defined as adverse events from the date of surgery up to 30 days after surgery; <sup>c</sup>Data reported for the efficacy evaluable analysis set.

**Abbreviations:** TEAE, treatment-emergent adverse event.

**Example 4: Perioperative tislelizumab plus neoadjuvant chemotherapy for patients with resectable non-small-cell lung cancer**

[00553] Common approaches to treat patients with non-small-cell lung cancer (NSCLC) include surgery, radiation therapy, and chemotherapy.. Surgery offers the highest likelihood of curing resectable stage I, II, and IIIA NSCLC; however, the 5-year tumor recurrence rate can be as high as 67%, depending on disease stage. Adjuvant platinum-based chemotherapy remains the global standard of care for resectable, stage II–III NSCLC, although improvements in overall survival are modest and outcomes for these patients remain poor.

[00554] This study demonstrated significant improvements in event-free survival, major pathological response, and pathological complete response following perioperative tislelizumab combined with neoadjuvant chemotherapy. Hence, perioperative tislelizumab combined with neoadjuvant chemotherapy offered meaningful clinical benefit compared with neoadjuvant placebo plus chemotherapy. In the adjuvant setting, tislelizumab was administered at 400 mg on a 6-week cycle for up to eight cycles, providing a more flexible and convenient dosing schedule for patients than evaluated with other PD-(L)1 antibodies. This phase 3 trial evaluated an extended dose interval for anti-PD-(L)1 antibodies in the perioperative setting. Additionally, the safety profile of tislelizumab, both as monotherapy and when combined with chemotherapy, was manageable and consistent with the known safety profiles of the individual agents.

*Summary*

[00555] Adult patients with untreated stage II–IIIA NSCLC were randomized (1:1) to neoadjuvant tislelizumab 200 mg or placebo intravenously every 3 weeks, plus platinum-based doublet chemotherapy followed by surgery and adjuvant tislelizumab 400 mg or placebo every 6 weeks. Dual primary endpoints were major pathological response (MPR) rate and event-free survival (EFS). Safety was also assessed. Overall, 453 patients (median age 62·0 years [IQR 56·0–67·0], 410/453 [91%] male) were randomized to tislelizumab (n=226) or placebo (n=227). Median follow-up was 22·0 months (IQR 15·5–28·0). Tislelizumab significantly improved EFS versus placebo (stratified hazard ratio 56% [95% CI 0·40–0·79]; p=0·0003). MPR rate was significantly higher for tislelizumab: 56% (95% CI 50–63) versus 15% (95% CI 11–20) than placebo (difference 41% [95% CI 33–49]; p<0·0001). Grade  $\geq 3$  and serious treatment-related

adverse events (TRAEs) occurred in 163/226 (72%) and 35/226 (16%) patients who received tislelizumab, and 150/226 (66%) and 18/226 (8%) who received placebo. The most common grade  $\geq 3$  TRAE was decreased neutrophil count (tislelizumab, 138/226 [61%] vs placebo, 134/226 [59%]).

### *Methods*

[00556] The overall study design and patient inclusion criteria are set forth in Example 2 above and FIG. 5 shows the Trial Profile of this study update. Eligible patients were aged  $\geq 18$  years with previously untreated, histologically confirmed stage II - IIIA squamous or non-squamous NSCLC (according to the 8th edition of the American Joint Committee on Cancer/Union for International Cancer Control NSCLC staging system) and had no known EGFR mutation or ALK gene translocations, an evaluation by an attending thoracic surgeon to confirm eligibility for an R0 resection (no residual tumor) with curative intent, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 14 days before randomization. Men and women were eligible to participate in the study and patient sex was self-reported. A complete list of inclusion criteria is provided above in Example 2.

[00557] Patients were stratified by histology (squamous vs non-squamous), disease stage (II vs IIIA), and tumor PD-L1 expression (PD-L1  $\geq 1\%$  vs PD-L1  $<1\%$ /not evaluable/indeterminate) and were randomized 1:1 to the TIS (tislelizumab) or PBO placebo group. PD-L1 positive/negative was defined as patients with  $\geq 1\%$ / $<1\%$  of tumor cells with PD-L1 membrane staining assessed using the VENTANA® SP263 assay (Ventana Medical Systems, Inc., Tucson, AZ, USA) at a central laboratory. Permuted block-stratified randomization and concealed TIS or PBO allocation were performed using an interactive web response system, which was accessed by study site personnel to assign a unique number to each potential study participant. Double blinding was implemented to ensure that neither the investigator, patients, medical or ancillary medical staff, nor the sponsor staff and its designees were aware of which treatment (TIS vs PBO) was being administered in addition to chemotherapy. Emergency unblinding for AEs was permitted through an interactive web response system.

[00558] During the neoadjuvant phase, patients received three to four cycles of TIS 200 mg or

PBO intravenously every 3 weeks on day 1 plus platinum-based doublet chemotherapy (squamous: cisplatin/carboplatin plus paclitaxel; non-squamous: cisplatin/carboplatin plus pemetrexed). Upon completion of neoadjuvant therapy, patients underwent curative-intent resection within 4–6 weeks of the last neoadjuvant dose. At 2–8 weeks after surgery, patients received adjuvant treatment with either intravenous PBO or TIS 400 mg every 6 weeks on day 1 for up to eight cycles. Postoperative radiotherapy was administered to some patients (i.e., those with positive tumor margins) before adjuvant treatment per standard medical practice; in these patients, adjuvant treatment was administered between 7 and 30 days after postoperative radiotherapy. Patients continued to receive treatment until disease recurrence or progression, unacceptable AEs, death, or until the maximum number of adjuvant cycles was complete, or either the patient and/or investigator decided to discontinue study treatment, whichever occurred first.

**[00559]** Scheduled tumor assessments were performed by computed tomography, positron emission tomography, and contrast-enhanced magnetic resonance imaging at screening, and then by computed tomography only within 14 days before cycle 3 of neoadjuvant treatment and surgery. After surgery, tumor assessments were performed every 3 months for the first 2 years, every 6 months from years 3–5, and then annually thereafter based on RECIST version 1.1. Tumor assessments continued until disease recurrence/progression was confirmed by blinded independent central review (BICR) per RECIST v1.1, withdrawal of consent, death, loss to follow-up, or study termination by the sponsor, whichever occurred first. Pathological response was assessed at a central laboratory in tumor tissue and lymph node tissue obtained from surgical resection. The percentage of viable tumor cells in  $\leq 1$  section per centimeter of tumor and lymph node tissue resected was evaluated.

**[00560]** Safety was assessed throughout the study by monitoring AEs (adverse events), serious AEs, and laboratory results. AEs and serious AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v5.0. Vital signs, physical examinations, change in ECOG performance status, electrocardiogram, and other examinations were also measured. Safety monitoring and review of interim efficacy data were performed by an independent data monitoring committee approximately every 6 months after the first patient was

randomized, or more frequently if indicated or requested by the medical monitor based on ongoing safety monitoring of patients on study. Safety follow-up was performed 30 days after the last dose of study treatment. Immune-mediated AEs were reported for up to 90 days after the last dose of TIS or PBO, regardless of whether the patient had started a new anti-cancer therapy. Follow-up of patients for survival status and subsequent anti-cancer treatment was done every 3 months ( $\pm 14$  days) via in-person or phone contact.

### *Analysis*

[00561] The dual primary endpoints were MPR rate, assessed by blinded independent pathology review (BIPR), and EFS, assessed by BICR, in the intention-to-treat (ITT) population. MPR rate was defined as the proportion of patients with  $\leq 10\%$  residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy in the ITT population. EFS was defined as the time from randomization until any of the following, whichever occurred first: disease progression precluding surgery according to RECIST v1.1, local or distant recurrence, or death due to any cause.

[00562] The key secondary endpoint was BIPR-assessed pCR rate, which was defined as the proportion of patients with absence of residual tumour in the resected primary tumour and all resected lymph nodes after completion of neoadjuvant therapy. Other secondary endpoints were OS, BICR- and investigator-assessed objective response rate per RECIST v1.1, BICR-assessed disease-free survival, investigator-assessed EFS (per RECIST v1.1), health-related quality of life, and safety and tolerability.

[00563] The sample size of approximately 450 patients was based on the number of events required to demonstrate EFS superiority of the TIS versus PBO group. Overall type I error was strongly controlled at a one-sided  $\alpha$  of 0.025. Initially, an  $\alpha$  of 0.005 and 0.02 were assigned to the primary hypothesis testing for MPR and EFS between the TIS and PBO groups, respectively. If MPR was statistically significant, then the  $\alpha$  of 0.005 was passed on to the hypothesis test of pCR; if the pCR comparison was statistically significant, then the  $\alpha$  of 0.005 was passed on to the hypothesis test of EFS, which was to be tested at a one-sided  $\alpha$  of 0.025. If the null hypotheses of MPR, pCR, and EFS were rejected, OS was sequentially tested with a recycled  $\alpha$  of 0.025. The interim analysis of OS was performed at the interim analysis of EFS with

Haybittle-Peto p-value boundary at 0.0001. A total of 184 EFS events were required to demonstrate efficacy in the ITT population, assuming a randomization ratio of 1:1 and the following: median EFS of 30 months in the PBO group and a one-sided  $\alpha$  of 0.02, 80% power to detect a hazard ratio (HR) of 0.65 (corresponding to an improvement in median EFS from 30 months to 46 months) in the EFS of the TIS group versus the PBO group. One interim analysis of EFS was planned when approximately 75% of the targeted EFS events had occurred, with Lan-DeMets alpha spending function approximation to the O'Brien-Fleming boundary.

[00564] pCR was tested after a statistically positive MPR result; the assumptions and powers under the sample size of 450 were as follows: for MPR, at one-sided  $\alpha$  of 0.005,  $\geq 95\%$  power to detect a 20% difference in MPR rate (40% vs 20%); for pCR, a one-sided  $\alpha$  of 0.005 (if MPR was successful),  $\geq 95\%$  power to detect a 15% difference in pCR rate (19% vs 4%).

[00565] MPR and pCR were compared between treatment groups using the Cochran-Mantel-Haenszel test stratified by factors as previously described at randomization. The 95% confidence intervals (CIs) of MPR and pCR rates were computed using the Clopper-Pearson method. The Mantel-Haenszel common risk difference for MPR and pCR was estimated along with its 95% CIs constructed by a normal approximation and Sato's variance estimator stratified by factors as previously described at randomization. The Mantel-Haenszel common odds ratio (OR) for MPR and pCR was estimated along with its 95% CI constructed by a normal approximation of log OR and the Robins, Breslow, and Greenland variance estimate stratified by factors as previously described at randomization. In the subgroup analyses of MPR and pCR, the risk difference and its 95% CI were estimated using the same method without stratification factors. Kaplan-Meier methodology was also used to estimate the median (IQR) and the rate of EFS and OS at select time points. EFS and OS were compared between treatment groups using a stratified log-rank test, with HR and 95% CI estimated using a stratified Cox regression model. The 95% CIs for median EFS and OS were estimated using the Brookmeyer and Crowley method, and the 95% CIs for the EFS and OS rates were estimated using Greenwood's formula. In the subgroup analysis of EFS, the unstratified HR and 95% CI were estimated using a Cox regression model.

[00566] The ITT population included all randomized patients, and the safety population for the neoadjuvant and adjuvant phases included all randomized patients who received any amount



of TIS or PBO plus chemotherapy and any amount of TIS or PBO post-surgical resection, respectively. In the surgery phase, the safety population included all patients who received surgery. All calculations and analyses were conducted using SAS® v9.4 or higher. This trial is registered with ClinicalTrials.gov, NCT04379635.

### Results

[00567] A total of 453 patients in China were enrolled, with 226 and 227 patients randomized to the TIS and PBO groups, respectively; these patients comprised the ITT population (FIG. 5). Baseline and clinical characteristics of this population were similar and balanced between treatment groups (Table 14).

| Table 14: Baseline demographics and disease characteristics |                  |                  |
|-------------------------------------------------------------|------------------|------------------|
|                                                             | TIS<br>(n=226)   | PBO<br>(n=227)   |
| Age                                                         |                  |                  |
| Median (IQR), years                                         | 62·0 (57·0–67·0) | 63·0 (56·0–68·0) |
| ≥65 years                                                   | 83 (37)          | 98 (43)          |
| Sex                                                         |                  |                  |
| Male                                                        | 205 (91)         | 205 (90)         |
| Female                                                      | 21 (9)           | 22 (10)          |
| Asian race                                                  | 226 (100)        | 227 (100)        |
| ECOG performance status*                                    |                  |                  |
| 0                                                           | 142 (63)         | 154 (68)         |
| 1                                                           | 83 (37)          | 73 (32)          |
| Smoking status                                              |                  |                  |
| Current                                                     | 43 (19)          | 52 (23)          |
| Former                                                      | 150 (66)         | 138 (61)         |
| Never                                                       | 33 (15)          | 37 (16)          |
| Disease stage†                                              |                  |                  |
| II                                                          | 92 (41)          | 91 (40)          |
| IIIA                                                        | 132 (58)         | 133 (59)         |
| Histology‡                                                  |                  |                  |
| Squamous                                                    | 179 (79)         | 175 (77)         |
| Non-squamous                                                | 45 (20)          | 50 (22)          |
| Other                                                       | 2 (1)            | 2 (1)            |
| Clinical node status§                                       |                  |                  |
| N0                                                          | 60 (27)          | 54 (24)          |
| N1                                                          | 84 (37)          | 93 (41)          |

|                             |          |          |
|-----------------------------|----------|----------|
| N2                          | 82 (36)  | 79 (35)  |
| PD-L1 expression¶           |          |          |
| <1%                         | 89 (39)  | 84 (37)  |
| ≥1%                         | 130 (58) | 132 (58) |
| 1–49%                       | 59 (26)  | 70 (31)  |
| ≥50%                        | 71 (31)  | 62 (27)  |
| Not evaluable/indeterminate | 7 (3)    | 11 (5)   |

Data are n (%) unless otherwise specified. ECOG=Eastern Cooperative Oncology Group; IQR=interquartile range; PBO=placebo; PD-L1=programmed cell death ligand-1; TIS=tislelizumab. \*Data missing for one patient in the TIS group. †Disease stage IB (TIS group, n=1); stage IIIB (TIS group, n=1; PBO group, n=3). The patient with stage IB disease and the four patients with stage IIIB disease were incorrectly enrolled into the study. ‡As reported on the case report form; patients with mixed histology were categorised as “other”. § One patient in the PBO group was enrolled with N3. ¶PD-L1 positive/negative was defined as patients with ≥1%/<1% of tumour cells with PD-L1 membrane staining assessed using the VENTANA® SP263 assay (Ventana Medical Systems, Inc., Tucson, AZ, USA) at a central laboratory. PD-L1 not evaluable/indeterminate was defined as patients with insufficient sample quantity or quality to stain for PD-L1 status or those in whom PD-L1 status could not be determined despite appropriate amounts of tissue sample.

**[00568]** Overall median patient age was 62 years (IQR 56 • 0 – 67 • 0), with 40% aged ≥65 years. Most patients were male (410/453 [91%]), had an ECOG performance status of 0 (296/453 [65%]), and were former smokers (288/453 [64%]). In this study, 265/453 (59%) patients had stage IIIA disease and NSCLC histological characteristics were mostly squamous (354/453 [78%]). Overall, 262/453 (58%) patients had tumour with PD-L1 expression of ≥1%.

**[00569]** Median duration of follow-up for all patients was 22 months (IQR 15.5 – 28). Of 452/453 (>99%) patients who received ≥1 dose of neoadjuvant treatment (TIS, 226/226 [100%]; PBO, 226/227 [>99%]), 421 (93%) completed treatment (TIS plus chemotherapy, 211/226 [93%]; PBO plus chemotherapy, 210/226 [93%]) (FIG. 5). The median duration of exposure to TIS or PBO in the neoadjuvant phase was 9.6 weeks (IQR 9.0–12.1) and 9.4 weeks (IQR 9.0–12.1), respectively. In both groups, patients received a median of 3.0 cycles of treatment (IQR 3.0–4.0). In total, 363 patients (80%) underwent surgery (TIS, 190/226 [84%]; PBO, 173/226 [76%]). Lobectomy was the most common type of surgery (TIS, 135/190 [71%]; PBO, 106/173 [61%]). Among patients who underwent surgery, 181/190 (95%) in the TIS group and 161/173 (93%) in the PBO group had complete resection (R0).

**[00570]** In total, 315/453 (70%) patients received adjuvant treatment (TIS, 168/226 [74%];

PBO, 147/227 [65%]), and 207/453 (46%) patients completed adjuvant treatment (TIS, 106/226 [47%]; PBO, 101/227 [45%]). Nineteen of 453 (4%) patients were receiving adjuvant treatment at the data cutoff (TIS, 11/226 [5%]; PBO, 8/227 [4%]). In the adjuvant phase, median duration of exposure was 48.1 weeks (IQR 35.9–51.6) for TIS and 48.1 weeks (IQR 36.4–51.0) for PBO; in both groups, patients received a median of 8 cycles of treatment (IQR 6–8).

**[00571]** EFS by BICR in the ITT population significantly favoured the TIS group over the PBO group (stratified HR 0.56 [95% CI 0.40–0.79]; one-sided  $p=0.0003$ ) (FIG. 6A). Median EFS was not reached in either the tislelizumab (95% CI not estimable [NE]–NE) or placebo PBO (95% CI 16.6–NE) group. At 24 months, the EFS rate was 68.3% (95% CI 60.8–74.8) for the TIS group and 51.8% (95% CI 43.8–59.2) for the PBO group. The EFS benefit with TIS over PBO was generally consistent across prespecified subgroups (FIG. 6B). Of note, the EFS improvement with perioperative TIS over PBO was observed in patients with squamous (HR 0.56 [95% CI 0.38–0.83]) and non-squamous (0.64 [95% CI 0.32–1.26]), and was confirmed in those with stage II (HR 0.47 [95% CI 0.26–0.87]) and IIIA (HR 0.62 [95% CI 0.42–0.94]) disease.

**[00572]** A significant improvement in MPR rate was observed in the TIS group (127/226 [56%; 95% CI 50–63]) versus the PBO group (34/227 [15%; 95% CI 11–20]; difference 41% [95% CI 33–49]; one-sided  $p<0.0001$ ) (FIG. 7A). pCR rate was also significantly improved in the TIS versus PBO group (92/226 [41%; 95% CI 34–47] vs 13/227 [6%; 95% CI 3–10]; difference 35% [95% CI 28–42]; one-sided  $p<0.0001$ ) (FIG. 7B). The improvements in MPR and pCR rates favouring TIS versus PBO were maintained across prespecified subgroups (FIG. 7C and FIG. 8).

**[00573]** Thirty-one of 226 patients (14%) in the TIS group and 45/227 patients (20%) in the PBO group died during the study. A trend towards improved OS favouring the TIS group over the PBO group was observed, with a stratified HR of 0.62 (95% CI 0.39–0.98), although this did not reach statistical significance at this interim analysis ( $p=0.019$ ). Median OS was not reached in either treatment group (FIG. 9). The 24-month OS rate was 89% (95% CI 83–92) for the TIS group and 79% (95% CI 73–85) for the PBO group. Before surgery, complete and partial responses were observed in <1% and 71% of patients, respectively, in the TIS group and 1% and

54% of patients, respectively, in the PBO group.

**[00574]** Treatment-related AEs across all study phases were reported in 224/226 (99%) patients and 225/226 (>99%) patients in the TIS and PBO groups, respectively. Grade  $\geq 3$  treatment-related AEs and serious treatment-related AEs occurred in 163/226 (72%) and 35/226 (16%) patients who received TIS, respectively, and in 150/226 (66%) and 18/226 (8%) patients who received PBO. Treatment-related AEs led to death in four patients (2%) in the TIS group (one case each of infection, pneumonia, immune-mediated lung disease, and pneumonitis) and in two patients (1%) in the PBO group (one case each of respiratory tract haemorrhage and cardiac failure). Overall, treatment-related AEs led to discontinuation in 29/226 (13%) patients and 21/226 (9%) patients in the TIS and PBO groups, respectively. Treatment-related AE-related delays to surgery occurred for 5% of patients in the TIS group and 2% of patients in the PBO group, with the majority of delays not exceeding 2 weeks. The incidence rates of treatment-related AEs leading to surgery cancellation were very low in both groups, reported in <1% of patients. In both groups, the most common treatment-related AEs of any grade were decreased neutrophil count, decreased white blood cell count, and alopecia (Table 15).

| <b>Table 15: Treatment-related adverse events</b> |                        |                   |                        |                   |
|---------------------------------------------------|------------------------|-------------------|------------------------|-------------------|
|                                                   | <b>TIS<br/>(n=226)</b> |                   | <b>PBO<br/>(n=226)</b> |                   |
|                                                   | Any grade              | Grade 3 or higher | Any grade              | Grade 3 or higher |
| Neutrophil count decreased                        | 177 (78)               | 138 (61)          | 176 (78)               | 134 (59)          |
| White blood cell count decreased                  | 143 (63)               | 38 (17)           | 152 (67)               | 32 (14)           |
| Alopecia                                          | 106 (47)               | 1 (<1)            | 118 (52)               | 1 (<1)            |
| Anaemia                                           | 91 (40)                | 11 (5)            | 96 (43)                | 15 (7)            |
| Alanine aminotransferase increased                | 65 (29)                | 2 (1)             | 48 (21)                | 1 (<1)            |
| Nausea                                            | 60 (27)                | 1 (<1)            | 59 (26)                | 0                 |
| Aspartate aminotransferase increased              | 53 (24)                | 2 (1)             | 38 (17)                | 0                 |
| Platelet count decreased                          | 47 (21)                | 5 (2)             | 49 (22)                | 6 (3)             |
| Hypoaesthesia                                     | 44 (20)                | 0                 | 47 (21)                | 0                 |
| Decreased appetite                                | 40 (18)                | 1 (<1)            | 47 (21)                | 0                 |
| Rash                                              | 32 (14)                | 4 (2)             | 22 (10)                | 0                 |
| Hypothyroidism                                    | 31 (14)                | 2 (1)             | 5 (2)                  | 0                 |
| Arthralgia                                        | 30 (13)                | 1 (<1)            | 35 (16)                | 0                 |

| Table 15: Treatment-related adverse events |                |                   |                |                   |
|--------------------------------------------|----------------|-------------------|----------------|-------------------|
|                                            | TIS<br>(n=226) |                   | PBO<br>(n=226) |                   |
|                                            | Any grade      | Grade 3 or higher | Any grade      | Grade 3 or higher |
| Blood creatinine increased                 | 28 (12)        | 0                 | 26 (12)        | 0                 |
| Hyponatraemia                              | 28 (12)        | 1 (<1)            | 20 (9)         | 4 (2)             |
| Fatigue                                    | 27 (12)        | 1 (<1)            | 27 (12)        | 0                 |
| Constipation                               | 26 (12)        | 0                 | 24 (11)        | 0                 |
| Pain in extremity                          | 26 (12)        | 0                 | 29 (13)        | 0                 |
| Vomiting                                   | 21 (9)         | 0                 | 28 (12)        | 0                 |

**[00575]** Among patients who underwent surgery, 121/190 (64%) patients in the TIS group and 106/173 (61%) patients in the PBO group experienced AEs assessed as postoperative complications. Two patients (1%) in each group died within 30 days of undergoing surgery; three patients (1%) in the TIS group and four patients (2%) in the PBO group died within 90 days of undergoing surgery.

**[00576]** Immune-mediated AEs occurred in 90/226 (40%) patients who received TIS and 40/226 (18%) patients who received PBO. Grade  $\geq 3$  immune-mediated AEs were observed in 21/226 (9%) patients in the TIS group and 6/226 (3%) patients in the PBO group. The most common immune-mediated AE category was skin adverse reaction (TIS, 39/226 [17%]; PBO, 24/226 [11%]). Overall, 2/226 (1%) patients in the TIS group died due to immune-mediated pneumonitis; no deaths attributed to immune-mediated AEs occurred in the PBO group.

**[00577]** *Discussion:* This study demonstrated clinically meaningful and statistically significant improvements in EFS, MPR, and pCR in patients with resectable NSCLC who received perioperative TIS plus neoadjuvant chemotherapy versus those who received neoadjuvant chemotherapy. Improvements in EFS, MPR, and pCR favoring the TIS group were generally maintained across prespecified subgroups, including sex. Although baseline tumour burden at enrolment was balanced, a higher proportion of patients receiving invasive surgery was observed in the PBO group. This was due to the lower objective response rate in the PBO group before surgery (55%) than in the TIS group (71%). Surgical outcomes were similar between treatment groups, which suggests that the addition of neoadjuvant TIS to chemotherapy did not

impact the feasibility of surgery.

**[00578]** This study demonstrated significant differences in MPR rates (exceeding 40.0% [ $p < 0.0001$ ]) and pCR rates (35.0% [ $p < 0.0001$ ]) favouring the tislelizumab group.

**[00579]** The safety profile of TIS plus chemotherapy followed by surgery and adjuvant TIS was consistent with the safety profiles of the individual therapies. The incidence of grade  $\geq 3$  treatment-related AEs was comparable between both study groups, occurring in 72% of patients receiving TIS and in 66% of those receiving PBO. No new safety signals were identified. The incidence of treatment-related AEs was similar to that in previously reported trials of chemotherapy combined with checkpoint inhibitors, and most AEs were associated with chemotherapy (anaemia, nausea, and alopecia). The most common treatment-related AEs reported were decreased haematological indexes (neutrophil count, white blood cell count, and anaemia). The incidence and nature of immune-mediated AEs in patients who received TIS were consistent with prior reports,<sup>19</sup> with  $< 10\%$  of patients experiencing grade  $\geq 3$  immune-mediated AEs. The most common immune-mediated AEs were observed in the skin. Low and similar rates of deaths due to treatment-related AEs were seen in the two treatment groups (2% in the TIS group and 1% in the PBO group). Overall, the results show that perioperative TIS combined with neoadjuvant platinum-based chemotherapy has a manageable tolerability profile in resectable, early-stage NSCLC.

**[00580]** This study demonstrated that perioperative TIS plus neoadjuvant platinum-based chemotherapy provided a clinically meaningful and significant improvement in EFS, MPR, and pCR, accompanied by a trend toward an OS benefit, when compared with PBO plus neoadjuvant chemotherapy in resectable NSCLC. Furthermore, the safety profile of perioperative TIS plus chemotherapy was manageable and consistent with the known risks of each treatment. These findings support the use of perioperative TIS with neoadjuvant platinum-based chemotherapy for patients with resectable NSCLC.

**[00581]** Various references such as patents, patent applications, and publications are cited herein, the disclosures of which are hereby incorporated by reference herein in their entireties.

[00582] While certain embodiments have been illustrated and described, it should be understood that changes and modifications can be made therein in accordance with ordinary skill in the art without departing from the technology in its broader aspects as defined in the following claims.

[00583] The embodiments, illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms “comprising,” “including,” “containing,” etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the claimed technology. Additionally, the phrase “consisting essentially of” will be understood to include those elements specifically recited and those additional elements that do not materially affect the basic and novel characteristics of the claimed technology. The phrase “consisting of” excludes any element not specified.

[00584] The present disclosure is not to be limited in terms of the particular embodiments described in this application. Many modifications and variations can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and compositions within the scope of the disclosure, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the appended claims. The present disclosure is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled. It is to be understood that this disclosure is not limited to particular methods, reagents, compounds, or compositions, which can of course vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[00585] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[00586] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as “up to,” “at least,” “greater than,” “less than,” and the like, include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member.

[00587] All publications, patent applications, issued patents, and other documents referred to in this specification are herein incorporated by reference as if each individual publication, patent application, issued patent, or other document was specifically and individually indicated to be incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

[00588] Other embodiments are set forth in the following claims.



**What is claimed is:**

1. A method of treating a cancer in a subject in need thereof, wherein the cancer is a surgically resectable solid cancer, comprising:
  - (a) during a first treatment period parenterally administering to the subject a first dose of an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the first dose of the anti-PD-1 antibody is 200 mg once every three-weeks, and wherein the anti-PD-1 antibody comprises:
    - (i) a V<sub>H</sub> CDR1, V<sub>H</sub> CDR2, and a V<sub>H</sub> CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:31, 32 and 33, and
    - (ii) a V<sub>L</sub> CDR1, V<sub>L</sub> CDR2, and a V<sub>L</sub> CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:34, 35 and 36;
  - (b) after (i), surgically resecting the cancer of the subject; and during a second treatment period after (ii) parenterally administering to the subject a second dose of the anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the second dose of the anti-PD-1 antibody is 400 mg once every 6 weeks.
2. The method of claim 1, wherein the cancer is an early-stage cancer.
3. The method of claim 1, wherein the cancer is a Stage II or Stage IIIA cancer.
4. The method of claim 1, wherein the cancer is not locally advanced or metastatic.
5. The method of claim 1, wherein the cancer is breast, colon or a lung cancer.
6. The method of claim 5, wherein the cancer is non-small cell lung cancer (NSCLC).
7. The method of claim 6, wherein the cancer is squamous cell carcinoma.
8. The method of claim 6, wherein the cancer is non-squamous cell carcinoma.
9. The method of any one of claims 5-8, wherein the cancer is stage II or IIIA.

10. The method of any one of claims 5-9, wherein the cancer is not locally advanced or metastatic.
11. The method of any one of claims 1-10, wherein the heavy chain variable region of the anti-PD-1 antibody comprises the amino acid sequence of SEQ ID NO:24, and the light chain variable region of the anti-PD-1 antibody comprises the amino acid sequence of SEQ ID NO:26.
12. The method of claim 11, wherein the anti-PD-1 antibody comprises an IgG constant region comprising an amino acid sequence of SEQ ID NO:88.
13. The method of any one of claims 1-12, wherein the anti-PD-1 antibody is administered intravenously, optionally wherein the administration is by IV infusion.
14. The method of any one of claims 1-13, wherein the subject has not been previously treated for the cancer or the treatment is a first-line therapy.
15. The method of any one of claims 1-13, wherein the subject has not been previously treated with chemotherapy, radiotherapy and/or immunotherapy.
16. The method of any one of claims 1-13, wherein the treatment is a second line therapy.
17. The method of any one of claims 1-16, wherein the first treatment period comprises 3 or 4 cycles of three-weeks each.
18. The method of any one of claims 1-17, wherein the second treatment period comprises less than or equal to 8 cycles of six weeks each.
19. The method of any one of claims 1-17, wherein the second treatment period comprises at least 8 cycles of six weeks each.
20. The method of any one of claims 1-19, wherein the second treatment period starts within 8 weeks of the surgical resecting.
21. The method of any one of claims 1-20, wherein the surgical resecting is followed by radiotherapy before the start of the second treatment period.

22. The method of claim 21, wherein the radiotherapy is administered 30 to 60 days after the surgical resecting, and the second treatment period starts between 7 and 30 days after the radiotherapy.
23. The method of any one of claims 1-20, wherein the surgical resecting is not followed by radiotherapy.
24. The method of claim 23, wherein the second treatment period starts between 2 and 8 weeks after the surgical resection.
25. The method of any one of claims 1-24, wherein the first treatment period further comprises administering a therapeutically effective amount of one or more chemotherapeutic drugs.
26. The method of claim 25, wherein the one or more chemotherapeutic drugs comprises a platinum chemotherapy drug.
27. The method of claim 25 or 26, wherein the one or more chemotherapeutic drug is carboplatin or cisplatin.
28. The method of claim 27, wherein the cisplatin is administered intravenously at about 75 mg/m<sup>2</sup> or the carboplatin is administered intravenously at about area under the plasma or serum concentration-time curve 5 (AUC5), optionally wherein the administering is once every three-weeks (Q3W), optionally wherein the administration is by IV infusion.
29. The method of claim 25, wherein the one or more chemotherapeutic drug further comprises pemetrexed or paclitaxel, optionally wherein the pemetrexed is used when the NSLC is a non-squamous cell carcinoma and the paclitaxel is used when NSLC is a squamous cell carcinoma.
30. The method of claim 29, wherein the pemetrexed is administered intravenously at about 500 mg/m<sup>2</sup>, optionally wherein the administering is once every three-weeks (Q3W), optionally wherein the administration is by IV infusion.

31. The method of claim 29, when the paclitaxel is administered intravenously at about 175 mg/m<sup>2</sup>, optionally wherein the administering is once every three-weeks (Q3W), optionally wherein the administration is by IV infusion.
32. The method of any one of claims 1-31, wherein the treating is clinically effective or the subject is a responder to the treating by at least one measure of response to treatment.
33. The method of claim 32, wherein the response to treatment is measured by overall survival, progression-free or event-free survival, major pathological response (“MPR”), pathological complete response (“pCR”), overall response, partial response, duration of response, and/or tumor volume, diameter or size.
34. The method of claim 33, wherein subject is a responder as measured by MPR.
35. The method of claim 34, wherein the MPR is at least twice that observed in a control group of subjects not treated with the anti-PD-1 antibody.
36. The method of claim 34, wherein the subject has at least 25%, 35%, 40%, 45% or 50% probability of the MPR, or the treating is effective as demonstrated by patient population MPR of at least 25%, 35%, 40%, 45% or 50%.
37. The method of claim 33, wherein the response to treatment is measured by tumor volume, size or diameter, and wherein the treating reduces tumor volume, size or diameter in the subject by at least or more than 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90%.
38. The method of claim 33, wherein the subject is a responder by pCR, wherein the subject has at least 15%, 20%, 25%, 35%, or 40% probability of the pCR, or wherein the treating is effective as demonstrated by patient population pCR of at least 15%, 20%, 25%, 35%, or 40%.
39. The method of any one of claims 1-38, wherein the subject does not have an EGFR mutation, ROS1 mutation or an ALK gene translocation.

40. The method of claim 39, wherein the subject is EGFR negative for genomic tumor aberrations.
41. The method of claim 39, wherein the subject is negative for ALK genomic tumor aberrations.
42. The method of any one of claims 1-41, wherein the subject is a human.
43. The method of claim 42, wherein the human is an adult.
44. A method of treating a cancer in a subject in need thereof, wherein: the cancer is a solid cancer, and the solid cancer is selected from the group consisting of a lung cancer, a breast cancer, and esophageal cancer, and a colon cancer, the method comprises parenterally administering to the subject a dose of an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the dose is:
- (i) about 50 to 800 mg, or
  - (ii) about 2 mg/kg to about 5 mg/kg;
- and the anti-PD-1 antibody comprises:
- (a) a  $V_H$  CDR1,  $V_H$  CDR2, and a  $V_H$  CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:31, 32 and 33, and
  - (b) a  $V_L$  CDR1,  $V_L$  CDR2, and a  $V_L$  CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:34, 35 and 36.
45. A method of treating a cancer in a subject in need thereof, wherein the cancer is a solid cancer, comprising parenterally administering to the subject an anti-PD-1 antibody, or an antigen-binding fragment thereof, wherein the anti-PD-1 antibody is administered:
- (i) at a dose from about 50 to 800 mg, or
  - (ii) at a dose from about 2 mg/kg to about 5 mg/kg;
- and the anti-PD-1 antibody comprises:
- (a) a  $V_H$  CDR1,  $V_H$  CDR2, and a  $V_H$  CDR3 comprising amino acid sequences as set forth in SEQ ID NOs:31, 32 and 33, and
  - (b) a  $V_L$  CDR1,  $V_L$  CDR2, and a  $V_L$  CDR3 comprising amino acid sequences

as set forth in SEQ ID NOs:34, 35 and 36; and the method further comprises administering a therapeutically effective amount of chemotherapeutic drugs comprising (1) a platinum chemotherapy drug, or (2) carboplatin, and paclitaxel or nab-paclitaxel.

46. The method of claim 44, wherein the method further comprises administering a therapeutically effective amount of one or more chemotherapeutic drugs.

47. The method of claims 44 or 45, wherein the one or more chemotherapeutic drugs comprises a platinum chemotherapy drug.

48. The method of claims 45 or 46, wherein the one or more chemotherapeutic drugs comprises pemetrexed and a platinum chemotherapy drug.

49. The method of claims 47 or 48, wherein the platinum chemotherapy drug is carboplatin or cisplatin.

50. The method of claims 45 or 46, wherein the one or more chemotherapeutic drugs comprises (a) carboplatin, and (b) paclitaxel or nab-paclitaxel.

51. The method of any one of claims 44-50, wherein the cancer is a lung cancer, wherein the lung cancer is locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC), wherein the lung cancer is negative for epidermal growth factor receptor (EGFR) aberrations and anaplastic lymphoma kinase (ALK) genomic tumor aberrations, and the method further comprises administering pemetrexed and a platinum chemotherapy drug.

52. The method of any one of claims 44-51, wherein the cancer is locally advanced or metastatic squamous non-small cell lung cancer (NSCLC), and the method further comprises administering (a) carboplatin, and (b) paclitaxel or nab-paclitaxel.

53. The method of any one of claims 44-52, wherein the subject has not been previously treated for the cancer or the treatment is a first-line therapy.

54. The method of any one of claims 44-53, wherein the heavy chain variable region of the anti-PD-1 antibody comprises the amino acid sequence of SEQ ID NO:24, and the light chain variable region of the anti-PD-1 antibody comprises the amino acid sequence of SEQ ID NO:26.

55. The method of claim 54, wherein the anti-PD-1 antibody comprises an IgG constant region comprising an amino acid sequence of SEQ ID NO:88.

56. The method of any one of claims 44-55, wherein the anti-PD-1 antibody is administered intravenously, optionally wherein the administration is by IV infusion.

57. The method of claims 45, 49, 50, or 52, wherein the carboplatin is administered intravenously at about area under the plasma or serum concentration-time curve 5 (AUC5), optionally wherein the administering is once every three-weeks (Q3W), optionally wherein the administration is by IV infusion.

58. The method of claim 48, wherein the pemetrexed is administered intravenously at about 500 mg/m<sup>2</sup>, optionally wherein the administering is once every three-weeks (Q3W), optionally wherein the administration is by IV infusion.

59. The method of claim 50, wherein the paclitaxel is administered intravenously at about 175 mg/m<sup>2</sup>, optionally wherein the administering is once every three-weeks (Q3W), optionally wherein the administration is by IV infusion.

60. The method of any one of claims 44-59, wherein the anti-PD-1 antibody is administered at a dose from about 2 mg/kg to 5 mg/kg, optionally wherein the anti-PD-1 antibody is administered at a dose of about 2mg/kg Q3W, 5mg/kg Q3W or 200 mg Q3W, optionally wherein the anti-PD-1 antibody is administered at a dose of about 400 mg, optionally wherein the anti-PD-1 antibody is administered at a dose of about 150 mg Q2W, optionally wherein the anti-PD-1 antibody is administered at a dose of about 300 mg Q4W, and optionally wherein the anti-PD-1 antibody is administered at a dose of about 400 mg Q6W.

61. The method of any one of claims 44-59, wherein the anti-PD-1 antibody is administered at a dose from about 50 to 800 mg, optionally wherein the anti-PD-1 antibody is administered at

100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, or 800 mg.

62. The method of claim 61, wherein the PD-1 antibody is administered every week, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, or every 6 weeks, optionally wherein the anti-PD-1 antibody is administered at 150 mg every two weeks, 300 mg every four weeks, or 400 mg every six weeks.

63. The method of any one of claims 44-62, wherein the PD-1 antibody is administered prior to surgical removal of the solid cancer.

64. The method of any one of claims 44-62, wherein the PD-1 antibody is administered after surgical removal of the solid cancer.

65. The method of claim 63, wherein the PD-1 antibody is administered at a first dose prior to surgical removal of the solid cancer.

66. The method of claim 64, wherein the PD-1 antibody is administered at a second dose after surgical removal of the solid cancer.

67. The method of any one of claims 44-62, wherein the PD-1 antibody is administered at a first dose prior to surgical removal of the solid cancer, and wherein the PD-1 antibody is administered at a second dose after surgical removal of the solid cancer.

68. The method of any one of claims 64-67, wherein the first dose is:

(a) about 50 to 800 mg, optionally wherein the anti-PD-1 antibody is administered at 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, or 800 mg, or (ii) about 2 mg/kg to about 5 mg/kg; optionally wherein the first dose is 200 mg once every three-weeks (Q3W); and/or

wherein the second dose is:

(b) about 50 to 800 mg, optionally wherein the anti-PD-1 antibody is administered at 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg,



650 mg, 700 mg, 750 mg, or 800 mg, or (ii) about 2 mg/kg to about 5 mg/kg; optionally wherein the first dose is 400 mg once every six weeks (Q6W).

69. The method of any one of claims 44-68, wherein the solid cancer is an early-stage cancer.

70. The method of any one of claims 44-68, wherein the solid cancer is a Stage II or Stage IIIA cancer.

71. The method of any one of claims 44-68, wherein the solid cancer is not locally advanced or metastatic.

72. The method of any one of claims 44-68, wherein the solid cancer is breast, colon or a lung cancer.

73. The method of any one of claims 44-68, wherein the solid cancer is non-small cell lung cancer (NSCLC).

74. The method of any one of claims 44-68, wherein the solid cancer is squamous cell carcinoma.

75. The method of any one of claims 44-68, wherein the solid cancer is non-squamous cell carcinoma.

76. The method of any one of claims 72-75, wherein the solid cancer is stage II or IIIA.

77. The method of any one of claims 72-75, wherein the solid cancer is not locally advanced or metastatic.

78. The method any one of claims 44-68, wherein the solid cancer is esophageal squamous cell carcinoma.

79. The method of any one of claims 1-78, wherein the anti-PD-1 antibody is formulated in a pharmaceutical composition comprising a histidine buffer, a surfactant, and a stabilizer.

80. The method of claim 79, wherein the surfactant is a polysorbate.

81. The method of claims 79 or 80, wherein the stabilizer is trehalose.
82. A composition comprising an anti- PD-1 antibody for use in a method according to any one of claims 1-81.